TITLE OF THE INVENTION

B-SUPERFAMILY CONOTOXINS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application is related to U.S. provisional patent application Serial No. 60/264,323 filed on 29 January 2001, incorporated herein by reference, and claims priority thereto under 35 USC §119(e).

[0002] This invention was made with Government support under Grant No. PO1 GM48677 awarded by the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] The present invention is directed to β-superfamily conotoxin peptides (also referred to as β-conotoxins), derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives thereof and pharmaceutically acceptable salts thereof for the treatment of disorders associated with voltage-gated ion channels, ligand-gated ion channels and/or receptors. The invention is further directed to nucleic acid sequences encoding the conotoxin peptides and encoding propeptides, as well as the propeptides.

[0004] The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference, and for convenience are referenced in the following text by author and date and are listed alphabetically by author in the appended bibliography.

[0005] *Conus* is a genus of predatory marine gastropods (snails) which envenomate their prey. Venomous cone snails use a highly developed projectile apparatus to deliver their cocktail of toxic conotoxins into their prey. In fish-eating species such as *Conus magus* the cone detects the presence of the fish using chemosensors in its siphon. When close enough it extends its proboscis and impales the fish hollow harpoon-like tooth containing venom. This immobilizes the fish and enables the cone snail to wind it into its mouth via the tooth at the end of the proboscis. For general information on *Conus* and their venom see the website address http://grimwade.biochem.unimelb.edu.au/cone/referenc.html. Prey capture is accomplished through a sophisticated arsenal of peptides which target specific ion channel and receptor

subtypes. Each *Conus* species venom appears to contain a unique set of 50-200 peptides. The composition of the venom differs greatly between species and between individual snails within each species, each optimally evolved to paralyse it's prey. The active components of the venom are small peptides toxins, typically 10-30 amino acid residues in length and are typically highly constrained peptides due to their high density of disulphide bonds.

[0006] The venoms consist of a large number of different peptide components that when separated exhibit a range of biological activities: when injected into mice they elicit a range of physiological responses from shaking to depression. The paralytic components of the venom that have been the focus of recent investigation are the α-, ω- and μ-conotoxins. All of these conotoxins act by preventing neuronal communication, but each targets a different aspect of the process to achieve this. The α-conotoxins target nicotinic ligand gated channels, the μ-conotoxins target the voltage-gated sodium channels and the ω-conotoxins target the voltage-gated calcium channels (Olivera et al., 1985; Olivera et al., 1990). For example a linkage has been established between α-, αA- & ψ-conotoxins and the nicotinic ligand-gated ion channel; ω-conotoxins and the voltage-gated calcium channel; μ-conotoxins and the voltage-gated sodium channel; δ-conotoxins and the voltage-gated sodium channel; κ-conotoxins and the voltage-gated potassium channel; conantokins and the ligand-gated glutamate (NMDA) channel.

[0007] However, the structure and function of only a small minority of these peptides have been determined to date. For peptides where function has been determined, three classes of targets have been elucidated: voltage-gated ion channels; ligand-gated ion channels, and G-protein-linked receptors.

[0008] *Conus* peptides which target voltage-gated ion channels include those that delay the inactivation of sodium channels, as well as blockers specific for sodium channels, calcium channels and potassium channels. Peptides that target ligand-gated ion channels include antagonists of NMDA and serotonin receptors, as well as competitive and noncompetitive nicotinic receptor antagonists. Peptides which act on G-protein receptors include neurotensin and vasopressin receptor agonists. The unprecedented pharmaceutical selectivity of conotoxins is at least in part defined by a specific disulfide bond frameworks combined with hypervariable amino acids within disulfide loops (for a review see McIntosh et al., 1998).

[0009] There are drugs used in the treatment of pain, which are known in the literature and to the skilled artisan. See, for example, Merck Manual, 16th Ed. (1992). However, there is a demand for more active analgesic agents with diminished side effects and toxicity and which are

non-addictive. The ideal analgesic would reduce the awareness of pain, produce analgesia over a wide range of pain types, act satisfactorily whether given orally or parenterally, produce minimal or no side effects, be free from tendency to produce tolerance and drug dependence.

[0010] Due to the high potency and exquisite selectivity of the conopeptides, several are in various stages of clinical development for treatment of human disorders. For example, two *Conus* peptides are being developed for the treatment of pain. The most advanced is ω-conotoxin MVIIA (ziconotide), an N-type calcium channel blocker (see Heading, C., 1999; U.S. Patent No. 5,859,186). ω-Conotoxin MVIIA, isolated from *Conus magus*, is approximately 1000 times more potent than morphine, yet does not produce the tolerance or addictive properties of opiates. ω-Conotoxin MVIIA has completed Phase III (final stages) of human clinical trials and has been approved as a therapeutic agent. ω-Conotoxin MVIIA is introduced into human patients by means of an implantable, programmable pump with a catheter threaded into the intrathecal space. Preclinical testing for use in post-surgical pain is being carried out on another *Conus* peptide, contulakin-G, isolated from *Conus geographus* (Craig et al. 1999). Contulakin-G is a 16 amino acid O-linked glycopeptide whose C-terminus resembles neurotensin. It is an agonist of neurotensin receptors, but appears significantly more potent than neurotensin in inhibiting pain in *in vivo* assays.

[0011] In view of a large number of biologically active substances in *Conus* species it is desirable to further characterize them and to identify peptides capable of treating disorders voltage-gated ion channels, ligand-gated ion channels and/or receptors. Surprisingly, and in accordance with this invention, Applicants have discovered novel conotoxins that can be useful for the treatment of disorders involving voltage-gated ion channels, ligand-gated ion channels and/or receptors and could address a long felt need for a safe and effective treatment.

SUMMARY OF THE INVENTION

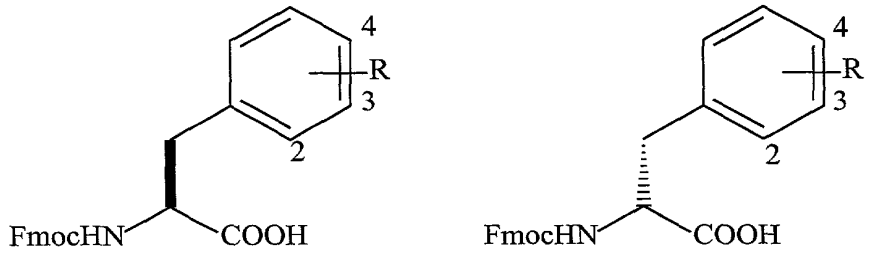
[0012] The present invention is directed to conotoxin peptides, derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives thereof and pharmaceutically acceptable salts thereof for the treatment of disorders associated with voltage-gated ion channels, ligand-gated ion channels and/or G-protein coupled receptors (GPCRs). The invention is further directed to nucleic acid sequences encoding the conotoxin peptides and encoding propeptides, as well as the propeptides.

[0013] More specifically, the present invention is directed to conotoxin peptides, having the amino acid sequences set forth in Tables 1-3 below. In the β-superfamily conotoxins containing 4-Cys residues (e.g., Ge14.1), the peptide may be bridged [1,4 / 2,3] or [1,3 / 2,4].

[0014] The present invention is also directed to derivatives or pharmaceutically acceptable salts of the conotoxin peptides or the derivatives. Examples of derivatives include peptides in which the Arg residues may be substituted by Lys, ornithine, homoarginine, *nor*-Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any synthetic basic amino acid. The Lys residues may be substituted by Arg, ornithine, homoarginine, *nor*-Lys, or any synthetic basic amino acid. The Tyr residues may be substituted with *meta*-Tyr, *ortho*-Tyr, *nor*-Tyr, ^{125}I-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any synthetic hydroxy containing amino acid. The Ser residues may be substituted with Thr or any synthetic hydroxylated amino acid. The Thr residues may be substituted with Ser or any synthetic hydroxylated amino acid. The Phe residues may be D or L, may be substituted at the *ortho*, *meta*, and/or *para* positions with a halogen or may be substituted with any synthetic aromatic amino acid. The Trp residues may be substituted with Trp (D), *neo*-Trp, 6-halo-Trp (D or L), preferably 6-halo, or any aromatic synthetic amino acid; and the Asn, Ser, Thr or Hyp residues may be glycosylated. The halogen may be iodo, chloro, fluoro or bromo; preferably iodo for halogen substituted-Tyr and bromo for halogen-substituted Trp. The Tyr residues may also be substituted with the 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic amino acid, e.g., tetrazolyl derivatives of Gly and Ala. The Leu may be substituted with Leu (D). The Glu residues may be substituted with Gla or Asp. The Gla residues may be substituted with Glu or Asp. The acidic amino acid residues may be substituted with any synthetic acidic amino acid, e.g. tetrazolyl derivatives of Gly and Ala. The N-terminal Gln may be substituted with pyro-glutamate (Z). The aliphatic amino acids may be substituted by synthetic derivatives bearing non-natural aliphatic branched or linear side chains C_nH_{2n+2} up to and including n=8. The Met residues may be substituted with *nor*-leucine (Nle). The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L). Basic residues in the backbone may be D or L configuration. The central Trp residue within the beta-turn is preferably epimerized to the D-form.

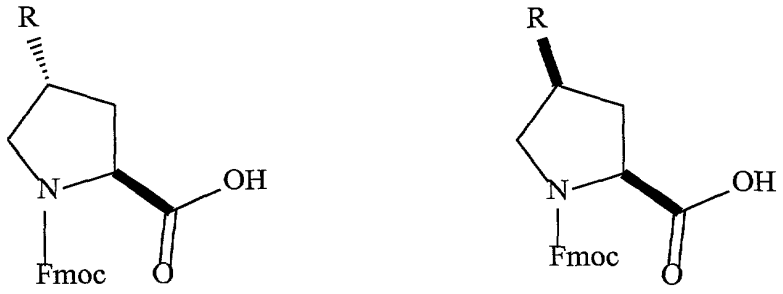
[0015] Examples of synthetic aromatic amino acid include, but are not limited to, nitro-Phe, 4-substituted-Phe wherein the substituent is C_1-C_3 alkyl, carboxyl, hyrdroxymethyl,

sulphomethyl, halo, phenyl, -CHO, -CN, -SO_3H and -NHAc. Examples of synthetic hydroxy containing amino acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of synthetic basic amino acids include, but are not limited to, N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolininyl)-Gly and 2-[3-(2S)pyrrolininyl)-Ala. These and other synthetic basic amino acids, synthetic hydroxy containing amino acids or synthetic aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino acids and aromatic amino acids and pages 66-87 for basic amino acids; see also http://www.amino-acids.com), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA. Examples of synthetic acid amino acids include those derivatives bearing acidic functionality, including carboxyl, phosphate, sulfonate and synthetic tetrazolyl derivatives such as described by Ornstein et al. (1993) and in U.S. Patent No. 5,331,001, each incorporated herein by reference, and such as shown in the following schemes 1-3.



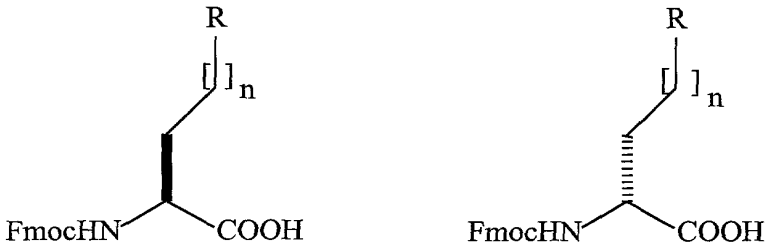
R=COOH, tetazole, CH_2COOH, 4-$NHSO_2CH_3$, 4-$NHSO_2$Phenyl, 4-CH_2SO_3H, SO_3H, 4-$CH_2PO_3H_2$, CH_2CH_2COOH, OCH_2Tetrazole, CH_2STetrazole, HNTetrazole, $CONHSO_2R_1$ where R_1 is CH_3 or Phenyl SO_2-Tetrazole, $CH_2CH_2SO_3H$, 1,2,4-tetrazole, 3-isoxazolone, amidotetrazole, $CH_2CH_2PO_3H_2$

Scheme 1



R = COOH, tetrazole, CH_2COOH, CH_2tetrazole

Scheme 2



R = COOH, tetazole, CH_2COOH, 4-$NHSO_2CH_3$, 4-$NHSO_2$Phenyl, 4-CH_2SO_3H, SO_3H, 4-$CH_2PO_3H_2$, CH_2CH_2COOH, OCH_2Tetrazole, CH_2STetrazole, HNTetrazole, $CONHSO_2R_1$ where R_1 is CH_3 or Phenyl SO_2-Tetrazole, $CH_2CH_2SO_3H$, 1,2,4-tetrazole, 3-isoxazolone, amidotetrazole, $CH_2CH_2PO_3H_2$; n = 0, 1, 2, or 3

Scheme 3

[0016] Additional derivatives are peptides in which the Asn residues may be modified to contain an N-glycan and the Ser, Thr and Hyp residues may be modified to contain an O-glycan (e.g., g-N, g-S, g-T and g-Hyp). In accordance with the present invention, a glycan shall mean any N-, S- or O-linked mono-, di-, tri-, poly- or oligosaccharide that can be attached to any hydroxy, amino or thiol group of natural or modified amino acids by synthetic or enzymatic methodologies known in the art. The monosaccharides making up the glycan can include D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, D-talose, D-galactosamine, D-glucosamine, D-N-acetyl-glucosamine (GlcNAc), D-N-acetyl-galactosamine

(GalNAc), D-fucose or D-arabinose. These saccharides may be structurally modified, e.g., with one or more O-sulfate, O-phosphate, O-acetyl or acidic groups, such as sialic acid, including combinations thereof. The gylcan may also include similar polyhydroxy groups, such as D-penicillamine 2,5 and halogenated derivatives thereof or polypropylene glycol derivatives. The glycosidic linkage is beta and 1-4 or 1-3, preferably 1-3. The linkage between the glycan and the amino acid may be alpha or beta, preferably alpha and is 1-.

[0017] Core O-glycans have been described by Van de Steen et al. (1998), incorporated herein by reference. Mucin type O-linked oligosaccharides are attached to Ser or Thr (or other hydroxylated residues of the present peptides) by a GalNAc residue. The monosaccharide building blocks and the linkage attached to this first GalNAc residue define the "core glycans," of which eight have been identified. The type of glycosidic linkage (orientation and connectivities) are defined for each core glycan. Suitable glycans and glycan analogs are described further in U.S. Serial No. 09/420,797 filed 19 October 1999 and in PCT Application No. PCT/US99/24380 filed 19 October 1999 (PCT Published Application No. WO 00/23092), each incorporated herein by reference. A preferred glycan is Gal(β1$\rightarrow$3)GalNAc(α1$\rightarrow$).

[0018] Derivatives also include peptides in which pairs of Cys residues may be replaced pairwise with isosteric lactam or ester-thioether replacements, such as Ser/(Glu or Asp), Lys/(Glu or Asp), Cys/(Glu or Asp) or Cys/Ala combinations. Sequential coupling by known methods (Barnay et al., 2000; Hruby et al., 1994; Bitan et al., 1997) allows replacement of native Cys bridges with lactam bridges. Thioether analogs may be readily synthesized using halo-Ala residues commercially available from RSP Amino Acid Analogues. In addition, individual Cys residues may be replaced with homoCys, seleno-Cys or penicillamine, so that disulfide bridges may be formed between Cys-homoCys or Cys-penicillamine, or homoCys-penicllamine and the like.

[0019] Derivatives and analogs also include truncations of the peptides disclosed herein. As used herein "truncations" are used to refer to peptides in which the sequence has been shortened from the mature conotoxin sequence that is predicted by the prepropeptide cleavage site with significant retention of activity of the native conotoxin. These truncations can be shortened from the N-terminus, the C-terminus, or both. As used herein significant retention of activity is used to refer to an activity of the truncated conotoxin which is less that 100-fold loss of activity and specificity.

[0020] Derivatives also include radiometal and chelated anti-tumor peptides. The incorporation of the radiometal eg ^{99m}Tc, ^{111}In, ^{90}Y, ^{188}Re, ^{105}RhS$_4$, ^{188}Re-tisuccin, , ^{89}Sr, ^{153}Sm, ^{186}Re, ^{67}Ga, ^{211}At, ^{212}Bi, ^{213}Bi, ^{177}Lu, ^{67}Cu, ^{64}Cu, ^{105}Rh, ^{47}Sc, ^{109}Pd] in to the conotoxin generally involves use of a chelate, specific to the particular metal, and a linker group to covalently attach the chelate to the conotoxin [the bifunctional chelate approach]. The design of useful chelates is dependent on the coordination requirements of the specific radiometal. DTPA, DOTA, P_2S_2-COOH BFCA requirement for kinetic TETA, NOTA are common egs. The requirement for kinetic stability of the metal complex is often achieved through the use of multidentate chelate ligands with a functionalised arm for covalent bonding to some part of the conotoxin ie the amino lysine group. Hence, the conotoxins of the present invention may be tagged to produce radiopharmaceuticals. In relation to radioligand probes of β-conotoxins for screening of small molecules, acting at unique allosteric sites, synthesis of such screening tools is not restricted to radioiodinated tyrosine derivatives. Incorporation of standard commercially available tritiated amino acid residues can also be utilized.

[0021] The present invention is further directed to a method of treating disorders associated with voltage-gated ion channels, ligand-gated ion channels and/or receptor disorders in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a conotoxin peptide described herein or a pharmaceutically acceptable salt or solvate thereof. The present invention is also directed to a pharmaceutical composition comprising a therapeutically effective amount of a conotoxin peptide described herein or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier.

[0022] More specifically, the present invention is also directed to nucleic acids which encode conotoxin peptides of the present invention or which encodes precursor peptides for these conotoxin peptides, as well as the precursor peptide. The nucleic acid sequences encoding the precursor peptides of other conotoxin peptides of the present invention are set forth in Table 1. Table 1 also sets forth the amino acid sequences of these precursor peptides.

[0023] Another embodiment of the invention contemplates a method of identifying compounds that mimic the therapeutic activity of the instant peptide, comprising the steps of: (a) conducting a biological assay on a test compound to determine the therapeutic activity; and (b) comparing the results obtained from the biological assay of the test compound to the results obtained from the biological assay of the peptide.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0024] The present invention is directed to β-superfamily conotoxin peptides (also referred to as β-conotoxins), derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives thereof and pharmaceutically acceptable salts thereof for the treatment of disorders associated with voltage-gated ion channels, ligand-gated ion channels and/or receptors, such as G-protein coupled receptors (GPCRs). The invention is further directed to nucleic acid sequences encoding the β-superfamily conotoxin peptides and encoding propeptides, as well as the propeptides.

[0025] The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of a β-superfamily conotoxin peptide, a mutein thereof, an analog thereof, a derivative thereof, an active fragment thereof or pharmaceutically acceptable salts or solvates. Such a pharmaceutical composition has the capability of acting at voltage-gated ion channels, ligand-gated ion channels and/or receptors (such as G-protein coupled receptors (GPCRs)), and are thus useful for treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the partial or complete blockade of such channels or receptors comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a pharmaceutical composition of the present invention.

[0026] G-protein-coupled receptors (GPCRs) are a large, upwards of 1000, and functionally diverse protein superfamily, which form a seven transmembrane (TM) helices bundle with alternating extra-cellular and intracellular loops. GPCRs are considered to be one of the most important groups of drug targets because they are involved in a broad range of body functions and processes and are related to major diseases. Over the last decades distinct members of the G Protein-Coupled Receptor (GPCR) family emerged as prominent drug targets within pharmaceutical research, since approximately 60% of marketed prescription drugs act by selectively addressing representatives of that class of transmembrane signal transduction systems. It is noteworthy that the majority of GPCR-targeted drugs elicit their biological activity by selective agonism or antagonism of biogenic monoamine receptors, while the development status of peptide-binding GPCR-addressing compounds is still in its infancy.

[0027] The β-conotoxins may function as allosteric modulators (i.e., agonists, partial agonists, neutral antagonists, inverse agonists) of GPCRs including, but not limited to, sst (sst_1,

sst_2, sst_3, sst_{2a}, sst_{2b}, sst_4, sst_5), cortistatin (CST), melanocortin (MC_xR, wherein x = 1, 2, 3, 4, 5), opioid (μ, δ, κ), neurokinin (NK_1, NK_2, NK_3), bradykinin (B_1, B_2), galanin (Gal_1, Gal_2, Gal_3), CCK_A, CCK_B, endothelin, serotonin, adrenergic receptors, angiotensin (AT_1, AT_2), neuropeptide-Y, sigma1, sigma2, oxytocin, CGRP, GRPR, histamine, imidazoline, neurotensin (NT_1, NT_2, NT_3), VIP, vasopressin (V1a, V1b, V2), substance K, chemokine receptors ($CXCR_1$, $CXCR_2$, $CXCR_3$, $CXCR_4$, $CXCR_5$, CCR_1, CCR_{2b}, CCR_3, CCR_4, CCR_5, CCR_6, CCR_7, CCR_8, CX_3CR_1), CRF_1, CRF_{2a}, CRF_{2b}, CRF_{2g}, CRF-BP orexin (Ox_1, Ox_2), urotensin (UT-II), glycoprotein IIb / IIIa, thrombin receptors, orphan GPCRs (eg. MCH_2R/SLT, SP1999/P_2Y_{12}, $CRTH_2$, $NPFF_1$, $NPFF_2$, HH_4R, h-GPR_{54}, $CysLT_2$, neuromedin receptors, $BLTR_2$, G_2A, TA_1, LTB_4, ghrelin, motilin MTL-R, purinergic receptors, muscarinic receptors, ORL-1, apelin, CB_1, CB_2 and the like). For an extensive list of GPCRs see http://www.gpcr.org/7tm/htmls/_entries.html. For additional orphan GPCR references see Shaaban (2001) and Civelli et. al. (2001). This beta turn toxin template may also be used to characterize new functional allosteric sites on known GPCRs. Radiolabelled dervatives serve as screening tools for such sites and will allow for identification of new small molecule modulators. The reverse beta turn motif serves as a template for beta turn peptidomimetic design in which the turn template contains the cone snail WK recognition "fingerprint", examples of such templates can be found in Golebiowski et al. (2001), Horwell (1996) and Beeley (2000).

[0028] Somatostatin Receptors (SSTRs): Somatostatin (SRIF), was first identified as a peptide that inhibits growth hormone release. Later it was shown to have other physiological activities, including the inhibition of the release of many endocrine secretions such as prolactin, TSH and insulin. The peptide also exhibits neuromodulatory functions and may act as a neurotransmitter. Somatostatin has two major actions; inhibition of hormone and cytokine (IFN-γ, IL-6, IL-8, IL-1) release and inhibition of cellular proliferation. SRIF can inhibit the release of hormones in the brain and almost all hormone release in the gut, together with many cytokines and growth factors eg PDGF. SRIF can be produced in cells from neuroendocrine and immune systems. It is produced in two forms SRIF-28 and SRIF-14. Additionally a novel SST-like peptide called cortistatin (CST) has been isolated from human. CST-14 shares 11 of the 14 amino acids with SRIF. One measurable difference between SRIF and CST is that SRIF increases the duration of REM sleep in rats whereas CST decreases it. It is thus possible to postulate that specific CST receptors exist .

[0029] Five sst receptors have been identified sst1, 2, 3, 4, 5. All are GPCRs and are encoded on a different chromosome. Both SRIF-14 and SRIF-28 bind to all receptors but SRIF-28 has higher affinity for sst_5. It must be noted that 2 isoforms of sst_2 exist namely, sst_{2A} and sst_{2B}. SRIF receptors are widely expressed. Cells from the CNS, gut, pancreas, kidney, thyroid, lung and the immune system express the receptors in varying proportions.

[0030] Overproduction of growth factors from tumours can result in systemic effects, as seen in acromegaly, a chronic debilitating disease caused by excessive production of GH. SRIF analogs suppress the release of GH and thus can benefit patients. A majority of tumours originating from tissues naturally targeted by SRIF express sst receptors at high levels.

[0031] Synthetic peptides such as, lanreotide, octreotide and vapreotide bind sst_2 and 5 with high affinity and sst_3 to a lesser extent. . Not only have peptide analogs of SRIF been used to reduce tumour growth directly through somatostatin receptor signalling but also medicine finds considerable use for somatostatin receptors in tumour detection and imaging and now in tumour targeting (Slooter et al., 2001).

[0032] The high level expression of somatostatin receptors (SSTR) on various tumor cells has provided the molecular basis for successful use of radiolabeled octreotide/lanreotide analogs as tumor tracers in nuclear medicine, similar chemical; modifications of conotoxins bT2, bM1, bG1 may be achieved. The vast majority of human tumors seem to overexpress the one or the other of five distinct h-SSTR sub-type receptors. Whereas neuroendocrine tumors frequently overexpress h-$SSTR_2$, intestinal adenocarcinomas seem to over-express more often h-$SSTR_3$ or h-$SSTR_4$, or both of these h-SSTR. In contrast to ^{111}In-DTPA-DPhe1-octreotide (OCTREOSCAN) which binds to h-$SSTR_2$ and $_5$ with high affinity (K_d 0.1-5 nM), to h-$SSTR_3$ with moderate affinity (Kd 10-100 nM) and does not bind to h-$SSTR_1$ and h-$SSTR_4$, ^{111}In/^{90}Y-DOTA-lanreotide was found to bind to h-$SSTR_2$, $_3$, $_4$, and $_5$ with high affinity, and to h-$SSTR_1$ with lower affinity (K_d 200 nM). Based on its unique h-SSTR binding profile, ^{111}In-DOTA-lanreotide was suggested to be a potential radioligand for tumor diagnosis, and ^{90}Y-DOTA-lanreotide suitable for receptor-mediated radionuclide therapy. As opposed to ^{111}In-DTPA-DPhe1-octreotide and ^{111}In-DOTA-DPhe1-Tyr3-octreotide, discrepancies in the scintigraphic results were seen in about one third of (neuroendocrine) tumor patients concerning both the tumor uptake as well as detection of tumor lesions. On a molecular level, these discrepancies seem to be based on a "higher" high-affinity binding of ^{111}In-DOTA-DPhe1-Tyr3-octreotide to h-$SSTR_2$. Other somatostatin analogs with divergent affinity to the five known h-SSTR subtype

receptors have also found their way into the clinics, including ^{99}mTc-HYNIC-octreotide or ^{99}mTc-depreotide (NEOSPECT; NEOTECT).

[0033] Most of the imaging results are reported for neuroendocrine tumors (octreotide analogs) or non-small cell lung cancer (^{99}mTc-depreotide), indicating high diagnostic capability of this type of receptor tracers. Consequently to their use as receptor imaging agents, h-SSTR recognizing radioligands have also been implemented for experimental receptor-targeted radionuclide therapy. The study "MAURITIUS" (MulticenterAnalysis of a Universal Receptor Imaging and Treatment Initiative, a European Study), a Phase IIa study, showed in patients with a calculated tumor dose >10 Gy/GBq ^{90}Y-DOTA-lanreotide, the proof-of-principle for treating tumor patients with receptor imaging agents. Overall treatment results in > 60 patients indicated stable tumor disease in roughly 35% of patients and regressive disease in 15% of tumor patients with different tumor entities. No acute or chronic severe hematological toxicity, change in renal or liver function parameters due to ^{90}Y-DOTA-lanreotide, was reported. ^{90}In-DOTA-DPhe1-Tyr3-octreotide may show a higher tumor uptake in neuroendocrine tumor lesions and may therefore provide even better treatment results in tumor patients, but there is only limited excess to long-term and survival data at present. Besides newer approaches and recent developments of ^{188}Re-labeled radioligands no clinical results on the treatment response is available yet. In conclusion, several radioligands have been implemented on the basis of peptide receptor recognition throughout the last decade. A plentitude of preclinical data and clinical studies confirm "proof-of-principle" for their use in diagnosis as well as therapy of cancer patients. However, an optimal radiopeptide formulation does not yet exist for receptor-targeted radionuclide therapy (Virgolini, 2001).

[0034] During the last decade five different subtypes of melanocortin receptors have been identified and cloned, all of them are possible as new targets for drugs in the treatment of a number of clinical important conditions such as inflammatory diseases (MC_1-receptor agonists), MC_3/MC_4-receptors in the treatment of feeding disorder, agonists for treatment of obesity and antagonists for anorectic conditions. MC_3/MC_4-agonists or also assumed to be useful for treating sexual dysfunction. In the treatment of seborrheic dermatitis the MC_5 receptor is considered as a target. A number of peptide or peptide like ligands, agonists and/or antagonist has been discovered, however, most of them have a large similarity with the endogenous ligand α-MSH.

[0035] Melanocortins: The major source of melanocortins is the pituitary, where ACTH and β-lipotropin are the main products from the anterior pituitary, and α-MSH and β-lipotropin

are major products from the intermediate lobe. All melanocortins, i.e. α-Melanocyte stimulating hormone (α-MSH), β-MSH, γ-MSH and the endogenous opioid β-endorphin, are cleaved from POMC, but β-MSH and β-endorphin emanate from the C-terminal part of POMC, i.e. the β-lipotropin. γ-MSH is cleaved from the N-terminal part of POMC. While α-MSH is a tri-decapeptide proteolytically cleaved from proopiomelanocortin (POMC) comprising of the N-terminal part of ACTH and is considered as the endogenous ligand to the melanocortin receptors.

[0036] β-MSH is found in the hypothalamus, whereas γ-MSH is found in different areas of the CNS, adrenal medulla and neurons of the intestine. α-MSH has been demonstrated in the pituitary, but also in other parts of the CNS, as well as in peripheral parts of the body. Only low circulating concentrations of α-MSH have been detected in humans in normal situations, whereas the concentration is increased in several diseases.

[0037] Melanocortin Receptors MCRs: Melanocortin receptors belong to the family of G-protein coupled, 7-TM receptors, and have been identified in several tissues of the body. Today, 5 different subtypes of receptors, MC1-5, have been described. The MC_2 receptor binds only ACTH, and is present in the adrenal cortex and also in white adipose tissue of rodents, but not in man or primates. The MC_1, MC_2, MC_3, MC_4 and MC_5 receptors are distributed in different areas/organs of the body. The MC_2 receptor is not further discussed since it is considered as the ACTH receptor. Interestingly, the MC_3 receptor is expressed in low abundance during fetal life and expression increases to adult levels after birth, as demonstrated in rats. The opposite is true for the MC4 receptor, which is predominant during fetal life. However, both receptors seem to be important for different physiological functions postnatally.

[0038] The MC receptors and α-MSH are involved in several physiological functions besides affecting skin pigmentation. They have effects on learning, memory, behaviour, including sexual behaviour, regeneration in the neuromuscular system and protection from central nerve injury, cardiovascular functions, feeding and weight homeostasis, fever and immunomodulation/inflammation, exocrine functions and interact with opioids and dopamine. They are also ascribed effects such as regulation of the release of pituitary and peripheral hormone.

[0039] Examples of voltage-gated ion channels include the voltage-gated calcium channel, the voltage-gated sodium channel, the voltage-gated potassium channel and the proton-gated ion channel. Examples of ligand-gated channels include the nicotinic ligand-gated ion

channel, ligand-gated glutamate (NMDA) channel and the ligand-gated $5HT_3$ (serotonin) channel. Examples of receptors include the G-protein receptors. Activity of ψ-conotoxins is described in U.S. Patent No. 5,969,096 and in Shon et al. (1997). Activity of bromosleeper conotoxins is described in U.S. Patent No. 5,889,147 and in Craig et al. (1997). Activity of σ-conotoxins is described in U.S. Patent No. 5,889,147. Activity of contryphan conotoxins is described in U.S. Patent No. 6,077,934 and in Jimenez et al. (1996). Activity of conopressins is described in Cruz et al. (1987) and in Kruszynski et al. (1990). Activity of γ-conotoxins is described in Fainzilber et al. (1998). Activity of αA-conotoxins is described in Jacobsen et al. (1997) and in Hopkins et al. (1995). Activity of τ-conotoxins is described in U.S. Serial No. 09/497,491 (PCT/US00/03021, PCT published application WO 00/46371) as an antagonist for acetylcholine receptors and as analgesic agents for the treatment of pain (whether acute or chronic), including migraine, chronic pain, and neuropathic pain, without undesirable side effects. Activity of contulakins is described in U.S. Serial No. 09/420,797 (PCT/US99/24380, PCT published application WO 00/23092). Each of these references is incorporated herein by reference.

[0040] Since σ-conotoxins are antagonists of the $5HT_3$ receptor, they are also useful in treating irritable bowel syndrome (IBS) and visceral pain. Visceral pain is a common experience in health and disease. Chronic visceral hyperalgesia in the absence of detectable organic disease has been implicated in many common functional bowel disorders (FDB), such as IBS, non-ulcer dyspepsia (NUD) and non-cardiac chest pain (NCCP).

[0041] Pain in IBS cannot be explained by normal perception of abnormal motility. In the majority of patients, sensory perception itself is abnormal. Most visceral afferent information is part of the reflex activity of digestion and does not reach concious perception. Increasing evidence suggests that long term changes in the thresholds and gain of the visceral afferent pathways are present in patients with FDBs. This has been referred to as visceral hyperalgesia (Mayer et al., 1994).

[0042] It has been proposed that FDBs are a result of increased excitability of spinal neurones. According to their model, many inputs can result in transient, short term, or life long sensitization of afferent pathways involved in visceral reflexes and sensations from the gut. The increased sensory input to interneurons and / or dorsal horn neurons in the spinal cord will result in secondary hyperalgesia, in which adjacent, undamaged viscera develop sensitivity to normal innocuous stimuli (allodynia), and central hyperexcitability as a consequence of changes in the

circuitary of the dorsal horn. This central sensitization may subsequently extend to supraspinal centers also.

[0043] Altered spinal processing of visceral sensory information can explain altered sensory thresholds and altered referral patterns, the perception of visceral sensations without stimulation of visceral mechnoreceptors (sensation of incomplete evacuation), and the symptomatic involvement of multiple sites in the GI tract, including extra intestinal sites. Increased excitability of dorsal horn neurones, resulting in the recruitment of previously sub-threshold inputs, may explain cutaneous allodynia in some patients with IBS, burning sensations referred to different parts of the body, cold hypersensitivity and pain referral to upper and lower extremities.

[0044] A number of compounds have been shown to modulate visceral sensitivity in IBS patients. These include octreotide (sst_2; Novartis), the 5-HT_3 antgonists odansetron (Glaxo) and granisetron (SKB) and the peripheral kappa opioid agonist, fedotozine (Jouveinal SA). The 5-HT_3 antagonist alosteron (Glaxo), cuurrently in development for IBS, is active in modifying the perception of colonic distension and gut compliance in IBS patients. New drugs in development for the treatment of IBS that are targeted at pain control as well as dysmotility include 5-HT_3 and 5-HT_4 receptor antagonists. 5-HT_3 receptors are located throughout the central and peripheral nervous system – their role in modulating the activity of visceral afferent and enteric neurones has led to the proposal that 5-HT acts as a sensitizing agent via these receptors on visceral afferent neurones. 5-HT_3 receptor antagonists have been widely reported to attenuate blood pressure responses to intestinal distension. 5-HT_3 antagonists in development for IBS include Alosteron (phase III), which is reported to reduce abdominal pain, slow colonic transit and increase colon compliance in IBS patients. Other compounds with positive effects include the antiemetic Ramosteron (Yamanouchi), Cilansteron (Solvay) and YM-114 (Yamanouchi). An animal model for dysmotility of the GI tract has been described by Maric et al. (1989).

[0045] In addition to the above uses, the peptides of the present invention are also useful (i) for treating or diagnosis of cancer, neoplasm, solid tumor, diabetic nephropathy, fibrosis, hypophysis tumor, GI disease, IBS, restinosis, angiogenesis disorder, diabetes mellitus, endocrine tumor, diarrhea, pancreatic disease, prostate tumor, bleeding, apoptosis, inflammation, pain, diabetes, obesity, sexual dysfunction, acromegaly, glaucoma, cardiovascular, diabetic, retinopathy, depression, myocardial infarction, stroke, epilepsy, anorexia, wasting diseases, seborrheic dermatitis, schizophrenia, mood disorders, chemotherapeutic induced emesis,

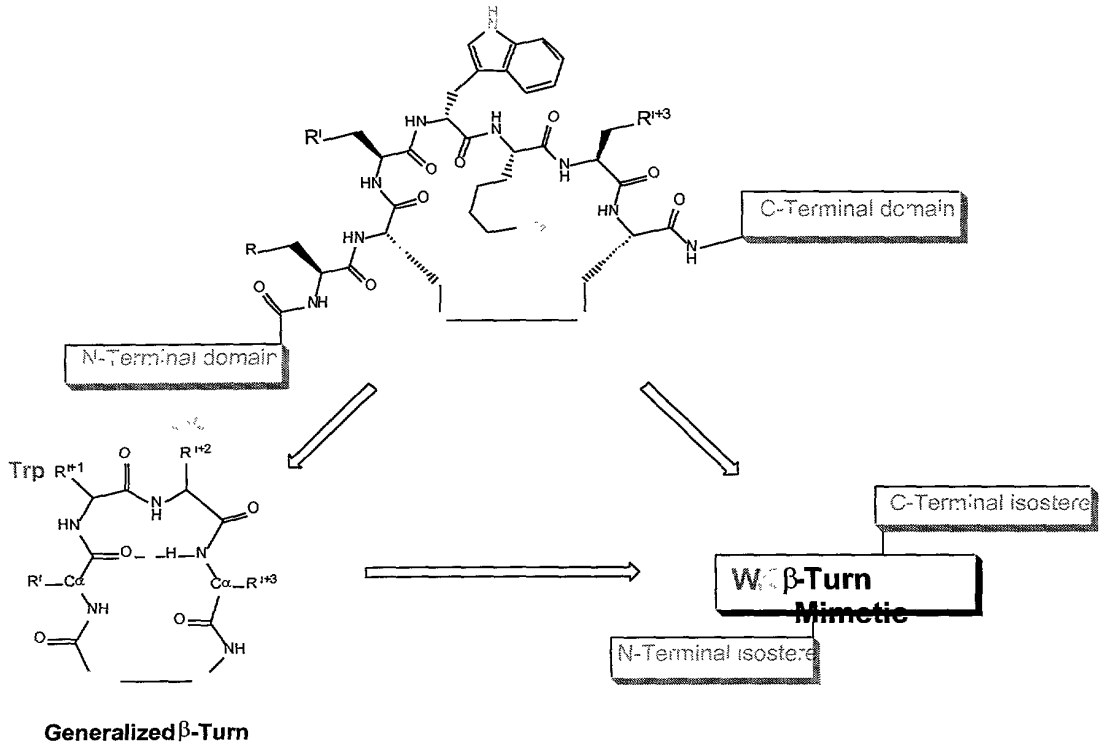
disorders associated with changes in blood pressure, immune disorders, nerve damage, acne, GI infections, myocardial infarction, angina, thromboembolism, cardiovascular disease, (ii) as templates for small molecule design and (iii) as screening tools.

[0046] The superfamily of seven-transmembrane-domain G-protein-coupled receptors (GPCRs) is the largest and most diverse group of transmembrane proteins involved in signal transduction. Each of the approximately 1000 family members found in vertebrates responds to stimuli as diverse as hormones, neurotransmitters, odorants and light, which selectively activate intracellular signaling events mediated by heterotrimeric G proteins. Because GPCRs are centrally positioned in the plasma membrane to initiate a cascade of cellular responses by diverse extracellular mediators, it is not surprising that modulation of GPCR function has been successful in the development of many marketed therapeutic agents. It has become clear that GPCRs for which a natural activating ligand has not yet been identified (orphan GPCRs) might provide a path to discovering new cellular substances that are important in human physiology. The process of 'de-orphanizing' these novel proteins has accelerated significantly and opened up new avenues for research in human physiology and pharmacology.

[0047] In most cases the extent of sequence homology is insufficient to assign these 'orphan' receptors to a particular receptor subfamily. Consequently, reverse molecular pharmacological and functional genomic strategies are being employed to identify the activating ligands of the cloned receptors. Briefly, the reverse molecular pharmacological methodology includes cloning and expression of orphan GPCRs in mammalian cells and screening these cells for a functional response to cognate or surrogate agonists present in biological extract preparations, peptide libraries, and complex compound collections. The functional genomics approach involves the use of "humanized" yeast cells, where the yeast GPCR transduction system is engineered to permit functional expression and coupling of human GPCRs to the endogenous signalling machinery. Both systems provide an excellent platform for identifying novel receptor ligands. Once activating ligands are identified they can be used as pharmacological tools to explore receptor function and relationship to disease.

[0048] The β-superfamily conotoxins can also be used to design a β-turn mimetic of the β-superfamily conotoxins containing a β-turn motif, e.g., the –CX1X2KX1C- (SEQ ID NO:338) motif where X1 is any amino acid and X2 is Trp in the D or L orientation (or halogenated at position 6 of the indole) or the –CPX3RVC- (SEQ ID NO:339) motif where X3 is Phe in the D or L configuration. Other β-turn motifs are also present in the β-superfamily conotoxins as

evident from the peptide sequences disclosed in Tables 2 and 3. This hairpin turn would be replaced by a non-peptide turn mimetic, preferably an orally available mimetic. The unique receptor binding domains contained within the N and C-terminal regions of the β-superfamily conotoxin would then be attached to the β-turn scaffold, in such a way as to mimic the 3D spatial array within the native toxin. As an example of the β-turn motif and a β-turn mimetic, see Scheme 4.



Scheme 4

[0049] The β-superfamily conotoxins of the present invention are also useful for characterizing sites on GPCRs and for identifying novel receptor ligands for GPCRS, especially orphan GCPRs. For example, the β-beta turn toxin template may also be used to characterize new functional allosteric sites on known GPCRs. Radiolabelled derivatives serve as screening tools for such sites and will allow for identification of new small molecule modulators. The reverse beta turn motif serves as a template for beta turn peptidomimetic design in which the turn template contains the cone snail WK recognition "fingerprint", examples of such templates

can be found in Golebiowski et al. (2001) and Horwell (2000). In addition, a ligand which binds to an orphan G-protein coupled receptor (orphan GPCR) can be identified by contacting a β-superfamily conotoxin with an orphan GPCR and measuring the amount of binding of the conotoxin to the orphan GPCR by methods that are well known in the art (Murphy et al., 1998). A homology search to identify other candidate ligands for testing can then be done on the basis of any peptide which binds to the orphan GPCR. The candidate ligands may be peptides or peptide mimetics.

[0050] The conotoxin peptides described herein are sufficiently small to be chemically synthesized. General chemical syntheses for preparing the foregoing conotoxin peptides are described hereinafter. Various ones of the conotoxin peptides can also be obtained by isolation and purification from specific *Conus* species using the technique described in U.S. Patent Nos. 4,447,356 (Olivera et al., 1984); 5,514,774; 5,719,264; and 5,591,821, as well as in PCT published application WO 98/03189, the disclosures of which are incorporated herein by reference.

[0051] Although the conotoxin peptides of the present invention can be obtained by purification from cone snails, because the amounts of conotoxin peptides obtainable from individual snails are very small, the desired substantially pure conotoxin peptides are best practically obtained in commercially valuable amounts by chemical synthesis using solid-phase strategy. For example, the yield from a single cone snail may be about 10 micrograms or less of conotoxin peptides peptide. By "substantially pure" is meant that the peptide is present in the substantial absence of other biological molecules of the same type; it is preferably present in an amount of at least about 85% purity and preferably at least about 95% purity. Chemical synthesis of biologically active conotoxin peptides peptides depends of course upon correct determination of the amino acid sequence.

[0052] The conotoxin peptides can also be produced by recombinant DNA techniques well known in the art. Such techniques are described by Sambrook et al. (1989). A gene of interest (i.e., a gene that encodes a suitable conotoxin peptides) can be inserted into a cloning site of a suitable expression vector by using standard techniques. These techniques are well known to those skilled in the art. The expression vector containing the gene of interest may then be used to transfect the desired cell line. Standard transfection techniques such as calcium phosphate co-precipitation, DEAE-dextran transfection or electroporation may be utilized. A wide variety of host/expression vector combinations may be used to express a gene encoding a

conotoxin peptide of interest. Such combinations are well known to a skilled artisan. The peptides produced in this manner are isolated, reduced if necessary, and oxidized to form the correct disulfide bonds.

[0053] One method of forming disulfide bonds in the conotoxin peptides of the present invention is the air oxidation of the linear peptides for prolonged periods under cold room temperatures or at room temperature. This procedure results in the creation of a substantial amount of the bioactive, disulfide-linked peptides. The oxidized peptides are fractionated using reverse-phase high performance liquid chromatography (HPLC) or the like, to separate peptides having different linked configurations. Thereafter, either by comparing these fractions with the elution of the native material or by using a simple assay, the particular fraction having the correct linkage for maximum biological potency is easily determined. However, because of the dilution resulting from the presence of other fractions of less biopotency, a somewhat higher dosage may be required.

[0054] The peptides are synthesized by a suitable method, such as by exclusively solid-phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution couplings.

[0055] In conventional solution phase peptide synthesis, the peptide chain can be prepared by a series of coupling reactions in which constituent amino acids are added to the growing peptide chain in the desired sequence. Use of various coupling reagents, e.g., dicyclohexylcarbodiimide or diisopropylcarbonyldimidazole, various active esters, e.g., esters of N-hydroxyphthalimide or N-hydroxy-succinimide, and the various cleavage reagents, to carry out reaction in solution, with subsequent isolation and purification of intermediates, is well known classical peptide methodology. Classical solution synthesis is described in detail in the treatise, "Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden," (1974). Techniques of exclusively solid-phase synthesis are set forth in the textbook, "Solid-Phase Peptide Synthesis," (Stewart and Young, 1969), and are exemplified by the disclosure of U.S. Patent 4,105,603 (Vale et al., 1978). The fragment condensation method of synthesis is exemplified in U.S. Patent 3,972,859 (1976). Other available syntheses are exemplified by U.S. Patents No. 3,842,067 (1974) and 3,862,925 (1975). The synthesis of peptides containing γ-carboxyglutamic acid residues is exemplified by Rivier et al. (1987), Nishiuchi et al. (1993) and Zhou et al. (1996).

[0056] Common to such chemical syntheses is the protection of the labile side chain groups of the various amino acid moieties with suitable protecting groups which will prevent a chemical reaction from occurring at that site until the group is ultimately removed. Usually also common is the protection of an α-amino group on an amino acid or a fragment while that entity reacts at the carboxyl group, followed by the selective removal of the α-amino protecting group to allow subsequent reaction to take place at that location. Accordingly, it is common that, as a step in such a synthesis, an intermediate compound is produced which includes each of the amino acid residues located in its desired sequence in the peptide chain with appropriate side-chain protecting groups linked to various ones of the residues having labile side chains.

[0057] As far as the selection of a side chain amino protecting group is concerned, generally one is chosen which is not removed during deprotection of the α-amino groups during the synthesis. However, for some amino acids, e.g., His, protection is not generally necessary. In selecting a particular side chain protecting group to be used in the synthesis of the peptides, the following general rules are followed: (a) the protecting group preferably retains its protecting properties and is not split off under coupling conditions, (b) the protecting group should be stable under the reaction conditions selected for removing the α-amino protecting group at each step of the synthesis, and (c) the side chain protecting group must be removable, upon the completion of the synthesis containing the desired amino acid sequence, under reaction conditions that will not undesirably alter the peptide chain.

[0058] It should be possible to prepare many, or even all, of these peptides using recombinant DNA technology. However, when peptides are not so prepared, they are preferably prepared using the Merrifield solid-phase synthesis, although other equivalent chemical syntheses known in the art can also be used as previously mentioned. Solid-phase synthesis is commenced from the C-terminus of the peptide by coupling a protected α-amino acid to a suitable resin. Such a starting material can be prepared by attaching an α-amino-protected amino acid by an ester linkage to a chloromethylated resin or a hydroxymethyl resin, or by an amide bond to a benzhydrylamine (BHA) resin or paramethylbenzhydrylamine (MBHA) resin. Preparation of the hydroxymethyl resin is described by Bodansky et al. (1966). Chloromethylated resins are commercially available from Bio Rad Laboratories (Richmond, CA) and from Lab. Systems, Inc. The preparation of such a resin is described by Stewart and Young (1969). BHA and MBHA resin supports are commercially available, and are generally used when the desired polypeptide being synthesized has an unsubstituted amide at the C-

terminus. Thus, solid resin supports may be any of those known in the art, such as one having the formulae -O-CH_2-resin support, -NH BHA resin support, or -NH-MBHA resin support. When the unsubstituted amide is desired, use of a BHA or MBHA resin is preferred, because cleavage directly gives the amide. In case the N-methyl amide is desired, it can be generated from an N-methyl BHA resin. Should other substituted amides be desired, the teaching of U.S. Patent No. 4,569,967 (Kornreich et al., 1986) can be used, or should still other groups than the free acid be desired at the C-terminus, it may be preferable to synthesize the peptide using classical methods as set forth in the Houben-Weyl text (1974).

[0059] The C-terminal amino acid, protected by Boc or Fmoc and by a side-chain protecting group, if appropriate, can be first coupled to a chloromethylated resin according to the procedure set forth in K. Horiki et al. (1978), using KF in DMF at about 60°C for 24 hours with stirring, when a peptide having free acid at the C-terminus is to be synthesized. Following the coupling of the BOC-protected amino acid to the resin support, the α-amino protecting group is removed, as by using trifluoroacetic acid (TFA) in methylene chloride or TFA alone. The deprotection is carried out at a temperature between about 0°C and room temperature. Other standard cleaving reagents, such as HCl in dioxane, and conditions for removal of specific α-amino protecting groups may be used as described in Schroder & Lubke (1965).

[0060] After removal of the α-amino-protecting group, the remaining α-amino- and side chain-protected amino acids are coupled step-wise in the desired order to obtain the intermediate compound defined hereinbefore, or as an alternative to adding each amino acid separately in the synthesis, some of them may be coupled to one another prior to addition to the solid phase reactor. Selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as a coupling reagent is N,N'-dicyclohexylcarbodiimide (DCC, DIC, HBTU, HATU, TBTU in the presence of HoBt or HoAt).

[0061] The activating reagents used in the solid phase synthesis of the peptides are well known in the peptide art. Examples of suitable activating reagents are carbodiimides, such as N,N'-diisopropylcarbodiimide and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide. Other activating reagents and their use in peptide coupling are described by Schroder & Lubke (1965) and Kapoor (1970).

[0062] Each protected amino acid or amino acid sequence is introduced into the solid-phase reactor in about a twofold or more excess, and the coupling may be carried out in a medium of dimethylformamide (DMF):CH_2Cl_2 (1:1) or in DMF or CH_2Cl_2 alone. In cases where

intermediate coupling occurs, the coupling procedure is repeated before removal of the α-amino protecting group prior to the coupling of the next amino acid. The success of the coupling reaction at each stage of the synthesis, if performed manually, is preferably monitored by the ninhydrin reaction, as described by Kaiser et al. (1970). Coupling reactions can be performed automatically, as on a Beckman 990 automatic synthesizer, using a program such as that reported in Rivier et al. (1978).

[0063] After the desired amino acid sequence has been completed, the intermediate peptide can be removed from the resin support by treatment with a reagent, such as liquid hydrogen fluoride or TFA (if using Fmoc chemistry), which not only cleaves the peptide from the resin but also cleaves all remaining side chain protecting groups and also the -amino protecting group at the N-terminus if it was not previously removed to obtain the peptide in the form of the free acid. If Met is present in the sequence, the Boc protecting group is preferably first removed using trifluoroacetic acid (TFA)/ethanedithiol prior to cleaving the peptide from the resin with HF to eliminate potential S-alkylation. When using hydrogen fluoride or TFA for cleaving, one or more scavengers such as anisole, cresol, dimethyl sulfide and methylethyl sulfide are included in the reaction vessel.

[0064] Cyclization of the linear peptide is preferably affected, as opposed to cyclizing the peptide while a part of the peptido-resin, to create bonds between Cys residues. To effect such a disulfide cyclizing linkage, fully protected peptide can be cleaved from a hydroxymethylated resin or a chloromethylated resin support by ammonolysis, as is well known in the art, to yield the fully protected amide intermediate, which is thereafter suitably cyclized and deprotected. Alternatively, deprotection, as well as cleavage of the peptide from the above resins or a benzhydrylamine (BHA) resin or a methylbenzhydrylamine (MBHA), can take place at 0°C with hydrofluoric acid (HF) or TFA, followed by oxidation as described above.

[0065] The peptides are also synthesized using an automatic synthesizer. Amino acids are sequentially coupled to an MBHA Rink resin (typically 100 mg of resin) beginning at the C-terminus using an Advanced Chemtech 357 Automatic Peptide Synthesizer. Couplings are carried out using 1,3-diisopropylcarbodimide in N-methylpyrrolidinone (NMP) or by 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and diethylisopropylethylamine (DIEA). The FMOC protecting group is removed by treatment with a 20% solution of piperidine in dimethylformamide(DMF). Resins are subsequently washed with DMF (twice), followed by methanol and NMP.

[0066] Muteins, analogs or active fragments, of the foregoing conotoxin peptides are also contemplated here. See, e.g., Hammerland et al. (1992). Derivative muteins, analogs or active fragments of the conotoxin peptides may be synthesized according to known techniques, including conservative amino acid substitutions, such as outlined in U.S. Patent Nos. 5,545,723 (see particularly col. 2, line 50--col. 3, line 8); 5,534,615 (see particularly col. 19, line 45--col. 22, line 33); and 5,364,769 (see particularly col. 4, line 55--col. 7, line 26), each herein incorporated by reference.

[0067] Radiolabeled peptides have been used to show that perhaps only the amino acid sequence actually involved in binding to the receptor is essential for achieving tumor uptake. ^{111}In-radiolabelled octreotide, which is used to image somatostatin positive tumors, is a prime example of this. In addition, advances in tumor biology have demonstrated metabolic pathways to deliver the nuclide within the cell cytoplasm through internalization mechanisms. Some classes of tumors have been shown to overexpress certain receptors, e.g., glutamate, AMPA, NMDA, somatostatin, melanocortin and the like, and whenever these substances can be radiolabeled and introduced to the system, they can become the lethal magic bullet by working inside the cell.

[0068] Specificity is the paramount goal in radionuclide therapy because with specificity comes safety and efficacy. The strategy in biologically targeted therapy is to chemically package the radionuclide to take advantage of metabolic pathways or tumor characteristics so that the radionuclide is localized in the target organ or tissue while the nuclear energy is discharged with minimal exposure to healthy tissue. The concentration differential of the therapeutic radio-pharmaceutical must be orders of magnitude between target and non-target tissues. Radiation doses of 4000 – 6000 rads are desirable in the target tissue, while only a few tens of radiation units can be functionally tolerated by some radiosensitive tissues. The short range of the emitted particles in the tissues makes them very damaging over the range in which their decay energy is deposited. The specificity of certain of the β-superfamily conotoxins for the somatostatin receptor provide the necessary specificity for the treatment and diagnosis of tumors.

[0069] Where the aim is to provide an image of the tumor, one will desire to use a diagnostic agent that is detectable upon imaging, such as a paramagnetic, radioactive or fluorogenic agent. Many diagnostic agents are known in the art to be useful for imaging purposes, as are methods for their attachment to peptides (see, e.g., U.S. Pat. Nos. 5,021,236 and 4,472,509, both incorporated herein by reference). In the case of paramagnetic ions, one might

mention by way of example ions such as chromium (III), manganese (II), iron (III), iron (II), cobalt (II), nickel (II), copper (II), neodymium (III), samarium (III), ytterbium (III), gadolinium (III), vanadium (II), terbium (III), dysprosium (III), holmium (III) and erbium (III), with gadolinium being particularly preferred. Ions useful in other contexts, such as X-ray imaging, include but are not limited to lanthanum (III), gold (III), lead (II), and especially bismuth (III). Moreover, in the case of radioactive isotopes for therapeutic and/or diagnostic application, one might mention ^{131}iodine, ^{123}iodine, ^{99m}technicium, ^{111}indium, ^{188}rhenium, ^{186}rhenium, ^{67}gallium, ^{67}copper, ^{90}yttrium, ^{125}iodine, or ^{211}astatine. Short-lived positron emission tomography (PET) isotopes, such as ^{18}flourine, can also be used for labeling peptides for use in tumor diagnosis (Okarvi, 2001).

[0070] Where the aim is to treat the tumor, one will desire to use a radionuclide that will irradiate the tumor. Suitable radionuclides include ^{131}iodine, ^{123}iodine, ^{99m}technicium, ^{111}indium, ^{188}rhenium, ^{186}rhenium, ^{67}gallium, ^{90}yttrium, ^{105}rhodium, ^{89}strontium, ^{153}samarium, ^{211}astatine, ^{212}bismuth, ^{213}bismuth, ^{177}lutetium, ^{67}copper, ^{47}scandium, ^{109}palladium. Optimally, radionuclides are chosen for the specific application on the basis of physical and chemical properties such that (a) their decay mode and emitted energy are matched to the delivery site, (b) their half life and chemical properties are complementary to the biological processing and (c) production methods can yield the radionuclide at the necessary level of specific activity and radionuclide purity.

[0071] The incorporation of the radiometal into the β-superfamily conotoxins generally involves use of a chelate, specific to the particular metal, and a linker group to covalently attach the chelate to the conotoxin, i.e., a the bifunctional chelate approach. The design of useful chelates is dependent on the coordination requirements of the specific radiometal. DTPA, DOTA, P_2S_2-COOH BFCA requirement for kinetic TETA, NOTA are common examples. The requirement for kinetic stability of the metal complex is often achieved through the use of multidentate chelate ligands with a functionalized arm for covalent bonding to some part of the conantokin or γ-carboxyglutamate containing conopeptide, i.e., the lysine amino group. Techniques for chelating radioonuclides with proteins are well known in the art, such as demonstrated by interantional patent application publication No. WO 91/01144, incorporated herein by reference.

[0072] In some embodiments, the β-superfamily conotoxins are used in combination with one or more potentiators and/or chemotherapeutic agents for the treatment of cancer or tumors. An exemplary potentiator is triprolidine (U.S. Patent No. 5,114,951) or its cis-isomer

which are used in combination with chemotherapeutic agents. Another potentiator is procodazole, which is a non-specific immunoprotective agent active against viral and bacterial infections. Other potentiators which can be used with conantokins or γ-carboxyglutamate containing peptides and optionally another chemotherapeutic agent to treat or inhibit the growth of cancer include monensin, an anti-sense inhibitor of the RAD51 gene, bromodeoxyuridine, dipyridamole, indomethacin, a monoclonal antibody, an anti-transferrin receptor immunotoxin, metoclopramide, 7-thia-8-oxoguanosine, N-solanesyl-N,N'-bis(3,4-dimethoxybenzyl)ethylene-diamine, leucovorin, heparin, N-[4-[(4-fluorphenyl)sulfonly]phenyl] acetamide, heparin sulfate, cimetidine, a radiosensitizer, a chemosensitizer, a hypoxic cell cytotoxic agent, muramyl dipeptide, vitamin A, 2'-deoxycoformycin, a bis-diketopiperazine derivative, and dimethyl sulfoxide.

[0073] The chemotherapeutic agents which can be used with conantokins or γ-carboxyglutamate containing peptides and an optional potentiator are generally grouped as DNA-interactive agents, antimetabolites, tubulin-interactive agents, hormonal agents and others such as asparaginase or hydroxyurea. Each of the groups of chemotherapeutic agents can be further divided by type of activity or compound. The chemotherapeutic agents used in combination with γ-carboxy-glutamate containing peptides include members of all of these groups. For a detailed discussion of chemotherapeutic agents and their method of administration, see Dorr et al. (1994) and U.S. Patent No. 6290,929.

[0074] DNA-interactive agents include the alkylating agents, e.g. cisplatin, cyclophosphamide, altretamine; the DNA strand-breakage agents, such as bleomycin; the intercalating topoisomerase II inhibitors, e.g., dactinomycin and doxorubicin; the nonintercalating topoisomerase II inhibitors such as, etoposide and teniposde; and the DNA minor groove binder plicamydin. The alkylating agents form covalent chemical adducts with cellular DNA, RNA, and protein molecules and with smaller amino acids, glutathione and similar chemicals. Generally, these alkylating agents react with a nucleophilic atom in a cellular constituent, such as an amino, carboxyl, phosphate, sulfhydryl group in nucleic acids, proteins, amino acids, or glutathione.

[0075] The antimetabolites interfere with the production of nucleic acids by one or the other of two major mechanisms. Some of the drugs inhibit production of the deoxyribonucleoside triphosphates that are the immediate precursors for DNA synthesis, thus inhibiting DNA replication. Some of the compounds are sufficiently like purines or pyrimidines

to be able to substitute for them in the anabolic nucleotide pathways. These analogs can then be substituted into the DNA and RNA instead of their normal counterparts.

[0076] Tubulin interactive agents act by binding to specific sites on tubulin, a protein that polymerizes to form cellular microtubules. Microtubules are critical cell structure units. When the interactive agents bind on the protein, the cell cannot form microtubules. Tubulin interactive agents include colchicine, vincristine and vinblastine, both alkaloids and paclitaxel and cytoxan.

[0077] Hormonal agents are also useful in the treatment of cancers and tumors. They are used in hormonally susceptible tumors and are usually derived from natural sources. These include: estrogens, conjugated estrogens and ethinyl estradiol and diethylstilbesterol, chlortrianisen and idenestrol; progestins such as hydroxyprogesterone caproate, medroxyprogesterone, and megestrol; and androgens such as testosterone, testosterone propionate; fluoxymesterone, methyltestosterone. Adrenal corticosteroids are derived from natural adrenal cortisol or hydrocortisone. They are used because of their anti inflammatory benefits as well as the ability of some to inhibit mitotic divisions and to halt DNA synthesis. These compounds include, prednisone, dexamethasone, methylprednisolone, and prednisolone. Leutinizing hormone releasing hormone agents or gonadotropin-releasing hormone antagonists are used primarily the treatment of prostate cancer. These include leuprolide acetate and goserelin acetate. They prevent the biosynthesis of steroids in the testes. Antihormonal antigens include: antiestrogenic agents such as tamoxifen, antiandrogen agents such as flutamide; and antiadrenal agents such as mitotane and aminoglutethimide.

[0078] Pharmaceutical compositions containing a compound of the present invention as the active ingredient can be prepared according to conventional pharmaceutical compounding techniques. See, for example, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, PA). Typically, an antagonistic amount of active ingredient will be admixed with a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral, parenteral or intrathecally. For examples of delivery methods see U.S. Patent No. 5,844,077, incorporated herein by reference.

[0079] "Pharmaceutical composition" means physically discrete coherent portions suitable for medical administration. "Pharmaceutical composition in dosage unit form" means physically discrete coherent units suitable for medical administration, each containing a daily

dose or a multiple (up to four times) or a sub-multiple (down to a fortieth) of a daily dose of the active compound in association with a carrier and/or enclosed within an envelope. Whether the composition contains a daily dose, or for example, a half, a third or a quarter of a daily dose, will depend on whether the pharmaceutical composition is to be administered once or, for example, twice, three times or four times a day, respectively.

[0080] The term "salt", as used herein, denotes acidic and/or basic salts, formed with inorganic or organic acids and/or bases, preferably basic salts. While pharmaceutically acceptable salts are preferred, particularly when employing the compounds of the invention as medicaments, other salts find utility, for example, in processing these compounds, or where non-medicament-type uses are contemplated. Salts of these compounds may be prepared by art-recognized techniques.

[0081] Examples of such pharmaceutically acceptable salts include, but are not limited to, inorganic and organic addition salts, such as hydrochloride, sulphates, nitrates or phosphates and acetates, trifluoroacetates, propionates, succinates, benzoates, citrates, tartrates, fumarates, maleates, methane-sulfonates, isothionates, theophylline acetates, salicylates, respectively, or the like. Lower alkyl quaternary ammonium salts and the like are suitable, as well.

[0082] As used herein, the term "pharmaceutically acceptable" carrier means a non-toxic, inert solid, semi-solid liquid filler, diluent, encapsulating material, formulation auxiliary of any type, or simply a sterile aqueous medium, such as saline. Some examples of the materials that can serve as pharmaceutically acceptable carriers are sugars, such as lactose, glucose and sucrose, starches such as corn starch and potato starch, cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt, gelatin, talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol, polyols such as glycerin, sorbitol, mannitol and polyethylene glycol; esters such as ethyl oleate and ethyl laurate, agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline, Ringer's solution; ethyl alcohol and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations.

[0083] Wetting agents, emulsifiers and lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the

composition, according to the judgment of the formulator. Examples of pharmaceutically acceptable antioxidants include, but are not limited to, water soluble antioxidants such as ascorbic acid, cysteine hydrochloride, sodium bisulfite, sodium metabisulfite, sodium sulfite, and the like; oil soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, aloha-tocopherol and the like; and the metal chelating agents such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like.

[0084] For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The active agent can be encapsulated to make it stable to passage through the gastrointestinal tract while at the same time allowing for passage across the blood brain barrier. See for example, WO 96/11698.

[0085] For parenteral administration, the compound may be dissolved in a pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

[0086] A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing

clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, epidural, irrigation, intramuscular, release pumps, or infusion.

[0087] For example, administration of the active agent according to this invention may be achieved using any suitable delivery means, including:

(a) pump (see, e.g., Luer & Hatton (1993), Zimm et al. (1984) and Ettinger et al. (1978));

(b), microencapsulation (see, e.g., U.S. Patent Nos. 4,352,883; 4,353,888; and 5,084,350);

(c) continuous release polymer implants (see, e.g., U.S. Patent No. 4,883,666);

(d) macroencapsulation (see, e.g., U.S. Patent Nos. 5,284,761, 5,158,881, 4,976,859 and 4,968,733 and published PCT patent applications WO92/19195, WO 95/05452);

(e) naked or unencapsulated cell grafts to the CNS (see, e.g., U.S. Patent Nos. 5,082,670 and 5,618,531);

(f) injection, either subcutaneously, intravenously, intra-arterially, intramuscularly, or to other suitable site; or

(g) oral administration, in capsule, liquid, tablet, pill, or prolonged release formulation.

In one embodiment of this invention, an active agent is delivered directly into the CNS, preferably to the brain ventricles, brain parenchyma, the intrathecal space or other suitable CNS location, most preferably intrathecally.

[0088] Alternatively, targeting therapies may be used to deliver the active agent more specifically to certain types of cell, by the use of targeting systems such as antibodies or cell specific ligands. Targeting may be desirable for a variety of reasons, e.g. if the agent is unacceptably toxic, or if it would otherwise require too high a dosage, or if it would not otherwise be able to enter the target cells.

[0089] The active agents, which are peptides, can also be administered in a cell based delivery system in which a DNA sequence encoding an active agent is introduced into cells designed for implantation in the body of the patient, especially in the spinal cord region. Suitable delivery systems are described in U.S. Patent No. 5,550,050 and published PCT Application Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. Suitable DNA sequences can be prepared synthetically for each active agent on the basis of the developed sequences and the known genetic code.

[0090] Exemplary methods for administering compounds (e.g., so as to achieve sterile or aseptic conditions) will be apparent to the skilled artisan. Certain methods suitable for administering compounds useful according to the present invention are set forth in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 7th Ed. (1985). The administration to the patient can be intermittent; or at a gradual, continuous, constant or controlled rate. Administration can be to a warm-blooded animal (e.g. a mammal, such as a mouse, rat, cat, rabbit, dog, pig, cow or monkey); but advantageously is administered to a human being. Administration occurs after general anesthesia is administered. The frequency of administration normally is determined by an anesthesiologist, and typically varies from patient to patient.

[0091] The active agent is preferably administered in an therapeutically effective amount. By a "therapeutically effective amount" or simply "effective amount" of an active compound is meant a sufficient amount of the compound to treat the desired condition at a reasonable benefit/risk ratio applicable to any medical treatment. The actual amount administered, and the rate and time-course of administration, will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage, timing, etc., is within the responsibility of general practitioners or spealists, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of techniques and protocols can be found in *Remington's Pharmaceutical Sciences*.

[0092] Dosage may be adjusted appropriately to achieve desired levels, locally or systemically, and depending on use as a diagnostic agent or a therapeutic agent. For therapeutic uses, the active agents of the present invention typically exhibit their effect at a dosage range from about 0.001 mg/kg to about 250 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg of the active ingredient, more preferably from a bout 0.05 mg/kg to about 75 mg/kg. A suitable dose can be administered in multiple sub-doses per day. Typically, a dose or sub-dose may contain from about 0.1 mg to about 500 mg of the active ingredient per unit dosage form. A more preferred dosage will contain from about 0.5 mg to about 100 mg of active ingredient per unit dosage form. Dosages are generally initiated at lower levels and increased until desired effects are achieved. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous dosing over, for example 24

hours or multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

[0093] For diagnostic uses, an appropriate dosage will depend on the peptide and the detectable label. A suitable dose to be injected is in the range to enable imaging by scanning procedures known in the art. When a radiolabeled conantokin is used, it may be administered in a dose having a radioactivity of form 0.1 to 50 mCi, preferably, 0.1 to 30 mCi and more preferably, 0.1 to 20 mCi. For therpeutic uses, an appropriate dosage will depend on the peptide, the radionuculide, the size and location of the tumor and the half life of the active agent in the tumor. In general, the dose is calculated on the basis of of the radioactivity distribution to each organ and on observed target uptake. For example, the active agent may be administered at a daily dosage range having a radioactivity of from 0.1 to 3 mCi/kg, preferably 1 to 3 mCi/kg, more preferably 1 to 1.5 mCi/kg.

[0094] Advantageously, the compositions are formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredients. Tablets, coated tablets, capsules, ampoules and suppositories are examples of dosage forms according to the invention.

[0095] It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be consistent with the dosage form employed in single or multiple unit doses. The exact individual dosages, as well as daily dosages, are determined according to standard medical principles under the direction of a physician or veterinarian for use humans or animals.

[0096] The pharmaceutical compositions will generally contain from about 0.0001 to 99 wt. %, preferably about 0.001 to 50 wt. %, more preferably about 0.01 to 10 wt.% of the active ingredient by weight of the total composition. In addition to the active agent, the pharmaceutical compositions and medicaments can also contain other pharmaceutically active compounds. Examples of other pharmaceutically active compounds include, but are not limited to, analgesic agents, cytokines and therapeutic agents in all of the major areas of clinical medicine. When used with other pharmaceutically active compounds, the conopeptides of the present invention may be delivered in the form of drug cocktails. A cocktail is a mixture of any one of the compounds useful with this invention with another drug or agent. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, pump, injectable solution, etc.) would contain both the instant composition in combination supplementary potentiating agent. The individual drugs of the cocktail are each administered in therapeutically effective amounts. A

therapeutically effective amount will be determined by the parameters described above; but, in any event, is that amount which establishes a level of the drugs in the area of body where the drugs are required for a period of time which is effective in attaining the desired effects.

[0097] The present invention also relates to rational drug design for the indentification of additional drugs which can be used for the pursposes described herein. The goal of rational drug design is to produce structural analogs of biologically active polypeptides of interest or of small molecules with which they interact (e.g., agonists, antagonists, inhibitors) in order to fashion drugs which are, for example, more active or stable forms of the polypeptide, or which, e.g., enhance or interfere with the function of a polypeptide *in vivo*. Several approaches for use in rational drug design include analysis of three-dimensional structure, alanine scans, molecular modeling and use of anti-id antibodies. These techniques are well known to those skilled in the art. Such techniques may include providing atomic coordinates defining a three-dimensional structure of a protein complex formed by said first polypeptide and said second polypeptide, and designing or selecting compounds capable of interfering with the interaction between a first polypeptide and a second polypeptide based on said atomic coordinates.

[0098] Following identification of a substance which modulates or affects polypeptide activity, the substance may be further investigated. Furthermore, it may be manufactured and/or used in preparation, i.e., manufacture or formulation, or a composition such as a medicament, pharmaceutical composition or drug. These may be administered to individuals.

[0099] A substance identified as a modulator of polypeptide function may be peptide or non-peptide in nature. Non-peptide "small molecules" are often preferred for many *in vivo* pharmaceutical uses. Accordingly, a mimetic or mimic of the substance (particularly if a peptide) may be designed for pharmaceutical use.

[0100] The designing of mimetics to a known pharmaceutically active compound is a known approach to the development of pharmaceuticals based on a "lead" compound. This approach might be desirable where the active compound is difficult or expensive to synthesize or where it is unsuitable for a particular method of administration, e.g., pure peptides are unsuitable active agents for oral compositions as they tend to be quickly degraded by proteases in the alimentary canal. Mimetic design, synthesis and testing is generally used to avoid randomly screening large numbers of molecules for a target property.

[0101] Once the pharmacophore has been found, its structure is modeled according to its physical properties, e.g., stereochemistry, bonding, size and/or charge, using data from a range

of sources, e.g., spectroscopic techniques, x-ray diffraction data and NMR. Computational analysis, similarity mapping (which models the charge and/or volume of a pharmacophore, rather than the bonding between atoms) and other techniques can be used in this modeling process.

[0102] A template molecule is then selected, onto which chemical groups that mimic the pharmacophore can be grafted. The template molecule and the chemical groups grafted thereon can be conveniently selected so that the mimetic is easy to synthesize, is likely to be pharmacologically acceptable, and does not degrade *in vivo*, while retaining the biological activity of the lead compound. Alternatively, where the mimetic is peptide-based, further stability can be achieved by cyclizing the peptide, increasing its rigidity. The mimetic or mimetics found by this approach can then be screened to see whether they have the target property, or to what extent it is exhibited. Further optimization or modification can then be carried out to arrive at one or more final mimetics for *in vivo* or clinical testing.

[0103] The present invention further relates to the use of a labeled (e.g., radiolabel, fluorophore, chromophore or the like) of the β-conotoxins described herein as a molecular tool both *in vitro* and *in vivo*, for discovery of small molecules that exert their action at or partially at the same functional site as the native toxin and capable of elucidation similar functional responses as the native toxin. In one embodiment, the displacement of a labeled β-conotoxin from its receptor or other complex by a candidate drug agent is used to identify suitable candidate drugs. In a second embodiment, a biological assay on a test compound to determine the therapeutic activity is conducted and compared to the results obtained from the biological assay of a β-conotoxin. In a third embodiment, the binding affinity of a small molecule to the receptor of a β-conotoxin is measured and compared to the binding affinity of a β-conotoxin to its receptor.

[0104] In view of the targets of the β-conotoxins, they may be used for treating the following conditions: cancer (neoplasm, solid tumor, diabetic nephropathy, fibrosis, hypophysis tumor, GI disease, IBS, restinosis, angiogenesis disorder, diabetes mellitus, endocrine tumor, diarrhea, pancreatic disease, prostate tumor, bleeding, apoptosis), inflammation, pain, diabetes, obesity, sexual dysfunction, acromegaly, glaucoma, cardiovascular, diabetic, retinopathy, depression, myocardial infarction, stroke, epilepsy, anorexia, wasting diseases, seborrheic dermatitis, schizophrenia, mood disorders, chemotherapeutic induced emesis, disorders

associated with changes in blood pressure, immune disorders, nerve damage, acne, GI infections, myocardial infarction, angina, thromboembolism and cardiovascular disease.

[0105] The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, immunology, cell biology, cell culture and transgenic biology, which are within the skill of the art. See, e.g., Maniatis *et al.*, 1982; Sambrook *et al.*, 1989; Ausubel *et al.*, 1992; Glover, 1985; Anand, 1992; Guthrie and Fink, 1991; Harlow and Lane, 1988; Jakoby and Pastan, 1979; *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1984); *Transcription And Translation* (B. D. Hames & S. J. Higgins eds. 1984); *Culture Of Animal Cells* (R. I. Freshney, Alan R. Liss, Inc., 1987); *Immobilized Cells And Enzymes* (IRL Press, 1986); B. Perbal, *A Practical Guide To Molecular Cloning* (1984); the treatise, *Methods In Enzymology* (Academic Press, Inc., N.Y.); *Gene Transfer Vectors For Mammalian Cells* (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); *Methods In Enzymology*, Vols. 154 and 155 (Wu et al. eds.), *Immunochemical Methods In Cell And Molecular Biology* (Mayer and Walker, eds., Academic Press, London, 1987); *Handbook Of Experimental Immunology*, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); Riott, *Essential Immunology*, 6th Edition, Blackwell Scientific Publications, Oxford, 1988; Hogan et al., Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

EXAMPLES

[0106] The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

EXAMPLE 1

Isolation of DNA Encoding β-Superfamily Conopeptides

[0107] DNA coding for β-superfamily conotoxin peptides was isolated and cloned in accordance with conventional techniques using general procedures well known in the art, such as described in Olivera et al. (1996), including using primers based on the DNA sequence of known

conotoxin peptides. Alternatively, cDNA libraries was prepared from *Conus* venom duct using conventional techniques. DNA from single clones was amplified by conventional techniques using primers which correspond approximately to the M13 universal priming site and the M13 reverse universal priming site. Clones having a size of approximately 300-500 nucleotides were sequenced and screened for similarity in sequence to known conotoxins. The DNA sequences and encoded propeptide sequences are set forth in Table 1. DNA sequences coding for the mature toxin can also be prepared on the basis of the DNA sequences set forth in Table1. An alignment of the conopeptides of the present invention is set forth in Table 2. Sequences of truncated and analog peptides are set forth in Table 3.

TABLE 1

Sequences of β-Superfamily Conotoxins

Name: Fd14.1
Species: flavidus
Cloned: Yes

DNA Sequence:
GGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGC
CCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGCCAGATGA
CTTAACCCCACAGCTTATTTTGCAAAGTCTGGATTCCCGTCGTCATGATCACGGCAT
TCGTCCGAAGAGAGTCGACATATGTAACTGGAGGATATGTGCACCAAACCCATTGA
GACGACATGATCTTAAGAAAGGAAACAATTGACGTCAGACAACCGCCACAACTTGA
GTACGACATCGTTAATACGACTTCAGCAAATATGAAATTTTCAGCATCACTGTGGTT
GTGAAGAAATCAGTTGCTTTAAAAGGTTGGATTTGTCCTTGTTTAAGCCGTTGTACT
GATGACATCTCTGCACTATGAAATAAAGCTGATGTGACAAACTAAAAAAAAAAAAAA
AAAA (SEQ ID NO:1)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPDDLTPQLILQSLDSRRHDHGIRP
KRVDICNWRICAPNPLRRHDLKKGNN (SEQ ID NO:2)

Toxin Sequence:
His-Asp-His-Gly-Ile-Arg-Xaa3-Lys-Arg-Val-Asp-Ile-Cys-Asn-Xaa4-Arg-Ile-Cys-Ala-Xaa3-
Asn-Xaa3-Leu-Arg-Arg-His-Asp-Leu-Lys-Lys-Gly-Asn-Asn-^ (SEQ ID NO:3)

Name: Mi14.1
Species: miles
Cloned: Yes

DNA Sequence:
GGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGGTGGGGCTCAC
CGTCGGGAGTCACGTCCATCGGTCTCACAGTCCTACATCGCGCAGCCATGGTGATGA
CTCCATTCATGACAAGACGATTCATCAACATCTGTTTGCCCGTCTTCCTCTGGAGAA
CAACGACGACCATCGTTCTGTGGATCTTCCTGCAGGGAATGGTGCAGGCAACACCA
AGCAACAAGACCAAAGTCCTCATCATGTGTGTTGTGCTATTGGTCCGGTTCTTCCAT
TCTGTTGTGTCAGTTGGCTGCACAAACTCCATTGAACTGGCCAATGAAAATAACTCA
GGAATAGACAGAAAGGCAAAAAAAAAAAAAAAAA (SEQ ID NO:4)

Translation:
MQTAYWVMVMMMVVGLTVGSHVHRSHSPTSRSHGDDSIHDKTIHQHLFARLPLENND
DHRSVDLPAGNGAGNTKQQDQSPHHVCCAIGPVLPFCCVSWLHKLH (SEQ ID NO:5)

Toxin Sequence:
Xaa2-Gln-Asp-Gln-Ser-Xaa3-His-His-Val-Cys-Cys-Ala-Ile-Gly-Xaa3-Val-Leu-Xaa3-Phe-Cys-Cys-Val-Ser-Xaa4-Leu-His-Lys-Leu-His-^ (SEQ ID NO:6)

Name: Mi14.2
Species: miles
Isolated: No
Cloned: Yes

DNA Sequence:
GGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGGTGGGGTTCAC
CGTCGGGGGTCACGTCCATCGGTCTCACAGTCCTACATCGCGCAGCCATGGTGATGA
CTCCATTCATGACAAGACGATTCATCAACATCTGTTTGCCCGTCTTCCTCAGGAGAA
CAACGACGACCATCGTTCTGTGGATCTTCCTGCAGGGACTAGCGCAGGCGACATGA
AACCACAACGCCAAAGACGTCTCTGCTGCATCTTTGCCCCGATTCTTTGGTTCTGTT
GTCACGGTTAACAGCTCAAATTACACTGCACTGGCCGATTGAAAGAACTGCAATAA
ACGGAAAAAAAAAAAAAAAA (SEQ ID NO:7)

Translation:
MQTAYWVMVMMMVVGFTVGGHVHRSHSPTSRSHGDDSIHDKTIHQHLFARLPQENN
DDHRSVDLPAGTSAGDMKPQRQRRLCCIFAPILWFCCHG (SEQ ID NO:8)

Toxin Sequence:
Leu-Cys-Cys-Ile-Phe-Ala-Xaa3-Ile-Leu-Xaa4-Phe-Cys-Cys-His-# (SEQ ID NO:9)

Name: Cp14.1
Species: capitaneus
Cloned: Yes

DNA Sequence:

GGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGGTGGGGTTCAC
CGTCGGGGGTCACGTCCATCGGTCTCACAGTCCTACATCGCGCAGCCATGGTGATGA
CTCCATTCATGACGAGACGATTCATCAACATCTGTTTGCCCGTCTTCCTCAGGAGAA
CAACGACGACCATCGTTCTGTGGATCTTCCTGCAGGGACTAGCGCAGGCGACATGA
AACCACAACGCCAAAGAGGTTTCTGCTGCGACTTTCCCCCGATTTTTTGGTTCTGTT
GTATCGGTTAACAGCACAAATTACACTGCACTGGCCGATTGAAAGAACTGCAATAA
ACGGAAAAAAAA (SEQ ID NO:10)

Translation:
MQTAYWVMVMMMVVGFTVGGHVHRSHSPTSRSHGDDSIHDETIHQHLFARLPQENN
DDHRSVDLPAGTSAGDMKPQRQRGFCCDFPPIFWFCCIG (SEQ ID NO:11)

Toxin Sequence:
Gly-Phe-Cys-Cys-Asp-Phe-Xaa3-Xaa3-Ile-Phe-Xaa4-Phe-Cys-Cys-Ile-# (SEQ ID NO:12)

Name: Ge14.1
Species: generalis
Cloned: Yes

DNA Sequence:

GGATCCATGCAGACGGCCTACTGGGTAATGGTGATGATGATGGTGTGGATTAAAGG
CCCTGTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGCCAGACG
ACTTGACCCCAGTGTTTGCCTTGCATCATCCGGTTTCCCATCGTCGGTCTCACAGCA
GTAGTTTGTGGTGTGTATGTCCATTCAGGGTGTGTCCACCATGCCATGGAAGATGAC
CTGGTCCCAAACCAACAAAATAACGTCAGACAACCGCCACAACTTTAGTACGACAT
CCCTTAATACGACTTCAGCAAGTATTTTAACATCACTATGGTGTGATGAAATCAGTT
GCTTTAAAA (SEQ ID NO:13)

Translation:
MQTAYWVMVMMMVWIKGPVSEGGKLNDVIRGLVPDDLTPVFALHHPVSHRRSHSSSL
WCVCPFRVCPPCHGR (SEQ ID NO:14)

Toxin Sequence:
Ser-His-Ser-Ser-Ser-Leu-Xaa4-Cys-Val-Cys-Xaa3-Phe-Arg-Val-Cys-Xaa3-Xaa3-Cys-His-#
(SEQ ID NO:15)

Name: Wi14.1
Species: wittigi
Cloned: Yes

DNA Sequence:
ATGATGTTGGTGTGGATTACAGCCCCTCTGCCTGAAGGTGGTAAACTGAAGCACGT
AATTCGGGGTTTGGTGCCAGACGACTTAACCCCACAGCTTATCTTGCGAAGTCTGAT
TTCCCGTCGTAGTTCTGACGGCAGTGATCCGAAGGCAAAAAAACAGTGTATGTGGA

AGAGATGTATACCAGACCAATCGAGACTAGAAGAAGATGAATGATGTCAGACAAC
CGCCATCACTGTAGTATGACATCGTTAATACGACTTAAGCAAATATTTTAACATCAC
TGTGGTTCTGAAGACATCAGTTGCTTTAAAAGATTGGATTCTTCCTTGTTTAAGAGTT
GTACTGANATCATTCCTGCCCTGTGAAATAAAGCTGATGTTGACANNCAAACAAAA
AAAAAAAAAA (SEQ ID NO:16)

Translation:
MMLVWITAPLPEGGKLKHVIRGLVPDDLTPQLILRSLISRRSSDGSDPKAKKQCMWKRC
IPDQSRLEEDE (SEQ ID NO:17)

Toxin Sequence:
Ser-Ser-Asp-Gly-Ser-Asp-Xaa3-Lys-Ala-Lys-Lys-Gln-Cys-Met-Xaa4-Lys-Arg-Cys-Ile-Xaa3-Asp-Gln-Ser-Arg-Leu-Xaa1-Xaa1-Asp-Xaa1-^ (SEQ ID NO:18)

Name: Cn14.1
Species: consors
Cloned: Yes

DNA Sequence:
GGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGC
CCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGTCACACAT
CTTAATCCCACAGCATACCTTGCGAAGTCTGACTTCCCGTGATCGTTCTGACAACGG
TGGTTCGAGTGGAGCACAAATATGCATCTGGAAGGTATGTCCACCATCCCCATAGA
GACGACCACGAGGAAAAAGATGAACGGCGTCAGACAACCGCCACAACTGTAGTAC
GACATCGTTGATACGACTTCAGCAACTATTTTAACATCACTGTGGTTGTGAAGAAAT
CAGTCGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCT
GCACTATGAAATAAAGCTGATGTGACATAAAAAAAAAAAAAAAAAGTACTCTGCGT
TGTTACTCGAG (SEQ ID NO:19)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVSHILIPQHTLRSLTSRDRSDNGGSS
GAQICIWKVCPPSP (SEQ ID NO:20)

Toxin Sequence:
Asp-Arg-Ser-Asp-Asn-Gly-Gly-Ser-Ser-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-^ (SEQ ID NO:21)

Name: Cn14.2
Species: consors
Cloned: Yes

DNA Sequence:
GGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGC
CCCTCTGTCTGAAGGTGGTAAATTGAACGACGCAATTCGGGGTTTGGTGTCACACAT
CTTAATCCCACAGCATACCTTGCGAAGTCTGACTTCCCGTGCTCGTTCTGACAACGG

TGGTTCGAGTGGAGCACAAATATGCATCTGGAAGGTATGTCCACCATCCCCATGGA
GACGACCACAAGGAAAAAGATGAATGACGTCAGACAACCGCCACAACTGTAGTAC
GACATCGTTGATACGACTTCAGCAAATATTTTAACATCACTGTGGTTGTGAAGAAAT
CAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCT
GCACTATGAAATAAAGCTGATGTGACAAACAATAAAAAAGAAAAAAAAAAAAGTA
CTCTGCGTTGTTACTCGAG (SEQ ID NO:22)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDAIRGLVSHILIPQHTLRSLTSRARSDNGGSS
GAQICIWKVCPPSPWRRPQGKR (SEQ ID NO:23)

Toxin Sequence:
Ala-Arg-Ser-Asp-Asn-Gly-Gly-Ser-Ser-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-Arg-Xaa3-Gln-# (SEQ ID NO:24)

Name: Cn14.3
Species: consors
Cloned: Yes

DNA Sequence:
GGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGC
CCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGCCACACTT
CTTAACCCCACAGCATATCTTGCAAAGTCTGACTTCCCGTAATGGTTCTGGCAGCAG
TAATCAGAAAGAAGCACAACTATGCATCTGGAAGGTATGTCCACCATCCCCATGGA
GATGACCACAAGGAAAAAGATGAACGGCGTCAGACAACCGCCACAACTGTAGTGG
GACATCGTTGATACGACTTCAGCAAATATTTTAACATCACTGTGGTTGTGAAGAAAT
CAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAATTGTACTGATATCAGCTCT
GCACTATGAAATAAAGCTGATGTGACAACCCAAAAAAAAAAAAAAAAAAAAGTAC
TCTGCGTTGTTACTCGAG (SEQ ID NO:25)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPHFLTPQHILQSLTSRNGSGSSNQ
KEAQLCIWKVCPPSPWR (SEQ ID NO:26)

Toxin Sequence:
Asn-Gly-Ser-Gly-Ser-Ser-Asn-Gln-Lys-Xaa1-Ala-Gln-Leu-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-^ (SEQ ID NO:27)

Name: T14.1
Species: tulipa
Cloned: Yes

DNA Sequence:
GGATCCATGCAGACGGCCTACTGGGTGATGCTGATGATGATGGTGTGGATTACAGC
CCCTCTGTCTGAAGGTGGTAAACTGAACGACGTAATTCGGGGTTTGGTGCCACACGT

CTTAACCCCACAGCATATCTTGCAAAGTCTGGTTTCCCGTCGTCATTTTAACAGCGTT
GTTCCGACGGTATACATATGCATGTGGAAGGTATGTCCACCATCGCCATAGAGACG
ACCATAAGGAAAAAGATGAATGACGTCAGACAACCGCCACAACTGTAGTACGACAT
CGTTAATACGACTTCAGCAAATATTTTAACATCACTGTGGTTGTGAAGAAATCAGTT
GCTTTAAAAGATTGGATTTTTCCTTGTTTCAGAGTTGTACTGATATCAGCTCTGCACT
ATCAAATAAAGCTGAAGTGACAAACCNNAAAAAAAAAAAAAAAAAAAAAAAAGTA
CTCTGCGTTGTTACTCGAG (SEQ ID NO:28)

Translation:

MQTAYWVMLMMMVWITAPLSEGGKLNDVIRGLVPHVLTPQHILQSLVSRRHFNSVVP
TVYICMWKVCPPSP (SEQ ID NO:29)

Toxin Sequence:

His-Phe-Asn-Ser-Val-Val-Xaa3-Thr-Val-Xaa5-Ile-Cys-Met-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-
Xaa3-^ (SEQ ID NO:30)

Name: T14.2
Species: tulipa
Isolated: No
Cloned: Yes

DNA Sequence:

ATGCAGACGGCCTACTGGGTGATGCTGTTGATGATGGTGGGCATTACAGCCCCTCTG
CCTGAAGGTGGTAAACCGAACAGCGTAATTCGGGGTTTGGTGCCAAACGACTTAAC
TCCACAGCATACCTTGCGAAGTCTGATTTCCCGTCGTCAAACTGACGTTCTTCTGGA
GGCTACCCTTTTGACAACACCAGCCCCCGAGCAGAGATTGTTCTGCTTCTGGAAGTC
ATGTTGGCCAAGGCCCTACCCTTGGAGACGACGTGATCTTAATGGAAAACGATGAA
TGACGTCAGACAACCGCCACAACTGTAGTACGACATCATTAATACGACTTCAGCAA
ATATTTTAACATTACTGTGGTTGTGAAGAAATCACTTGCTTTAAAAGATTGGTTTTTT
CCTTGTTTCAGAGTTGTACTGATATCAGCTCTGCCCTATGAAATAAAGCTGATG (SEQ
ID NO:31)

Translation:

MQTAYWVMLLMMVGITAPLPEGGKPNSVIRGLVPNDLTPQHTLRSLISRRQTDVLLEA
TLLTTPAPEQRLFCFWKSCWPRPYPWRRRDLNGKR (SEQ ID NO:32)

Toxin Sequence:

Xaa2-Thr-Asp-Val-Leu-Leu-Xaa1-Ala-Thr-Leu-Leu-Thr-Thr-Xaa3-Ala-Xaa3-Xaa1-Gln-Arg-
Leu-Phe-Cys-Phe-Xaa4-Lys-Ser-Cys-Xaa4-Xaa3-Arg-Xaa3-Xaa5-Xaa3-Xaa4-Arg-Arg-Arg-
Asp-Leu-Asn-# (SEQ ID NO:33)

Name: Sl14.2
Species: sulcatus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGTAAACCGAACGACGTAATTCGGGGTTTGGTGCCAGACGACTTAA
CCCCACAGCGTGTCTTGCGAAGTCTGATTTCCCGTCGTCAATCTGGCTGCAGAGTCC
CGTTTGAATTGAAATGCATCTGGAAGTTCTGTACAATATACCCATCGAGACCATTTG
CTTCTCTGGAAGAAAAAGACGAATGTCAGACAGTCACCATAACTGTAACATGGGAT
TTTTAATACGTCTCCAGCAAGTATTTTAACATCACTGTGGTTGTGAAGAAATCAGTT
GCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCTGCCCT
GTGAAATAAAGCTGATG (SEQ ID NO:34)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKPNDVIRGLVPDDLTPQRVLRSLISRRQSGCRVP
FELKCIWKFCTIYPSRPFASLEEKDECQTVTITVTWDF (SEQ ID NO:35)

Toxin Sequence:
Xaa2-Ser-Gly-Cys-Arg-Val-Xaa3-Phe-Xaa1-Leu-Lys-Cys-Ile-Xaa4-Lys-Phe-Cys-Thr-Ile-Xaa5-Xaa3-Ser-Arg-Xaa3-Phe-Ala-Ser-Leu-Xaa1-Xaa1-Lys-Asp-Xaa1-Cys-Gln-Thr-Val-Thr-Ile-Thr-Val-Thr-Xaa4-Asp-Phe-^ (SEQ ID NO:36)

Name: Sl14.1
Species: sulcatus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCTCTCTG
TCTGAAGGTGGTAAACCGAACGACGTCATTCGGGGTTTTGTGCCAGACGACTTAAC
CCCACAGCTTATCTTGCGAAGTCTGATTTCCCGTCGTCGTTCTGACAAGGATGTTGG
GAAGAGAATGGAATGTTACTGGAAGGCATGTAGACCCACGCTATCGAGACGACATG
ATCTTGGGTAAAAGATGAATGACGTCAGACAACAGCCACAACTATAGTATGACATC
GTTAATACGACTTCAGCAAATATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTG
CTTTAAAAGATTGGATTTTTCCGTGTTTAAGAGTTGTACTGATATCAGCTCTGCCCTG
TGAAATAAAGCTGATG (SEQ ID NO:37)

Translation:
MQTAYWVMVMMMVWITASLSEGGKPNDVIRGFVPDDLTPQLILRSLISRRRSDKDVGK
RMECYWKACRPTLSRRHDLG (SEQ ID NO:38)

Toxin Sequence:
Arg-Ser-Asp-Lys-Asp-Val-Gly-Lys-Arg-Met-Xaa1-Cys-Xaa5-Xaa4-Lys-Ala-Cys-Arg-Xaa3-Thr-Leu-Ser-Arg-Arg-His-Asp-Leu-# (SEQ ID NO:39)

Name: M14.1
Species: magus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGCTGATGATGATGGTGTGCATCACAGCCCCTCTG
CCTGAAGGTGGTAAACCGAACAGCGGAATTCGGGGTTTGGTGCCAAACGACTTAAC
TCCACAGCATACCTTGCGAAGTCTGATTTCCCGTCGTCAAACTGACGTTCTTCTGGA
TGCTACCCTTTTGACAACACCAGCCCCCGAGCAGAGATTGTTCTGCTTCTGGAAGTC
ATGTTGGCCAAGGCCCTACCCTTGGAGACGACGTAATCTTAATGGAAAACGATGAA
TGACGTCAGACAACCGCCACAACTGTAGTACGACATCGTTAATACGACTTCAGCAA
ATATTTTAACATAACTGTGGTTGTGAAGAAATCGGTTGCTTTAAAAGATTGGATTTT
TCCTTGTTTCAGAGTTGTACTGATATGAGCTCTGCCCTGTGAAATAAAGCTGATG
(SEQ ID NO:40)

Translation:
MQTAYWVMLMMMVCITAPLPEGGKPNSGIRGLVPNDLTPQHTLRSLISRRQTDVLLDA
TLLTTPAPEQRLFCFWKSCWPRPYPWRRRNLNGKR (SEQ ID NO:41)

Toxin Sequence:
Xaa2-Thr-Asp-Val-Leu-Leu-Asp-Ala-Thr-Leu-Leu-Thr-Thr-Xaa3-Ala-Xaa3-Xaa1-Gln-Arg-
Leu-Phe-Cys-Phe-Xaa4-Lys-Ser-Cys-Xaa4-Xaa3-Arg-Xaa3-Xaa5-Xaa3-Xaa4-Arg-Arg-Arg-
Asn-Leu-Asn-# (SEQ ID NO:42)

Name: Em14.1
Species: emaciatus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGCGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGCCAGATGACTTAA
CCCCACAGCTTGTTTTGCAAAGTCTGGATTCCCGTCGTCATACTCACGGCATTCGTC
CGAAGGGAGACGGCATATGTATCTGGAAGGTATGTCCACCAGACCCATGGAGACGA
CATCGTCTTAAGAAAAGAAACAATTGACGTCAGACAACCGCCACAACTTGAGTACG
ACATCGTTAATACGACTTCAGCAAATATGAAATTTTCAGCATCACTGTGGTTGTCAA
GAAATCAGTTGCTTTAAAAGATTGGATTTGTCCTTGTTTAAGAGTTGTACTGATGTC
AGCTCTGCCCTGTGAAATAAAGCTGATG (SEQ ID NO:43)

Translation:
MQTAYWVMAMMMVWITAPLSEGGKLNDVIRGLVPDDLTPQLVLQSLDSRRHTHGIRP
KGDGICIWKVCPPDPWRRHRLKKRNN (SEQ ID NO:44)

Toxin Sequence:
His-Thr-His-Gly-Ile-Arg-Xaa3-Lys-Gly-Asp-Gly-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-
Asp-Xaa3-Xaa4-Arg-Arg-His-Arg-Leu-Lys-Lys-Arg-Asn-Asn-^ (SEQ ID NO:45)

Name: Cr14.1

Species: circumcisus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGGTGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGTAAATCGAACGACGTAATTCGGGGTTTGGTGCCACACATCTTAA
CCCCACAGCATATCTTGCAAAGTCTGACTTCCCGTCTTCGTTCTGACAGCAGTGGTC
AGAAAGGAGCACAAATATGCATCTGGAAGGTATGTCCACTATCCCCATGGAGACGA
CCACAAGGAAAAAGATGAATGACGTCAGACAACCGCTACAACTGTAGTACGACATC
GTTGATACGACTTCAGCAAATATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTG
CTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCTGCCCTG
TGAAATAAAGCTGATG (SEQ ID NO:46)

Translation:
MQTAYWVMVMMVVWITAPLSEGGKSNDVIRGLVPHILTPQHILQSLTSRLRSDSSGQK
GAQICIWKVCPLSPWRRPQGKR (SEQ ID NO:47)

Toxin Sequence:
Leu-Arg-Ser-Asp-Ser-Ser-Gly-Gln-Lys-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Leu-
Ser-Xaa3-Xaa4-Arg-Arg-Xaa3-Gln-# (SEQ ID NO:48)

Name: Bt14.1
Species: betulinus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCCGAAGGTGGTAAACTGAACGATGTAATTCGGGCTTTGGCGCCAGACGACGTAA
CCCCACAGTTTATCTTGCGAAGTCTGATTTCCCGTCGTCGTTCTGACAGCGATGTTCG
GGAGGTACCCGTATGTTCCTGGAAGATATGTCCACCATAGCCATAGAGACGACATG
ATCTTAAGGAAAAAGAGAAATGACGTCAGACAACCGCCACAACTGTAGTACGGCAT
CGTTAATACGACTTCAGCAAATGTTTTAACATCACTGTGGTTGTGAAGAAATCAGCT
GCTTTAAAAGATTGGATTTTTCCTTAAGAGTTGCACTGATGTCAGTTCTGCCCTGTG
AAATAAAGCTGATG (SEQ ID NO:49)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRALAPDDVTPQFILRSLISRRRSDSDVRE
VPVCSWKICPP (SEQ ID NO:50)

Toxin Sequence:
Arg-Ser-Asp-Ser-Asp-Val-Arg-Xaa1-Val-Xaa3-Val-Cys-Ser-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-^
(SEQ ID NO:51)

Name: A14.1

Species: aurisiacus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGCGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGCCAGATGACTTAA
CCCCACAGCTTGTTTTGCAAAGTCTGGATTCCCGTCGTCATACTCACGGCATTCGTC
CGAAGGGAGACGGCATATGTATCTGGAAGGTATGTCCACCAGACCCATGGAGACGA
CATCATCTTAAGAAAAGAAACAATTGACGTCAGACAACCGCCACAACTTGAGTACG
ACATCGTTAATACGACTTCAGCAAATATGAAATTTTCAGCATCACTGTGGTTGTCAA
GAAATCAGTTGCTTTAAAAGATTGGATTTGTCCTTGTTTAAGAGTTGTACTGATGTC
AGCTCTGCCCTATGAAATAAAGCTGATG (SEQ ID NO:52)

Translation:
MQTAYWVMAMMMVWITAPLSEGGKLNDVIRGLVPDDLTPQLVLQSLDSRRHTHGIRP
KGDGICIWKVCPPDPWRRHHLKKRNN (SEQ ID NO:53)

Toxin Sequence:
His-Thr-His-Gly-Ile-Arg-Xaa3-Lys-Gly-Asp-Gly-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-
Asp-Xaa3-Xaa4-Arg-Arg-His-His-Leu-Lys-Lys-Arg-Asn-Asn-^ (SEQ ID NO:54)

Name: A14.2
Species: aurisiacus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGTAAATTGAACGACGTAATTTGGGGTTTGGTGCCACACATCTTAAC
CCCACAGCATATCTTGCAAAGCCTGACTTCCCGTCTTCATTCTGACAGCAGTGATCA
GAAAGGAGGCATGAACGCATGGACAGGAGCAGGAGCACAAATATGCATCTGGAAG
GTATGTCCACCACCCCCATGGAGATGAACACAAGGAAAAAGATGAATGACGTCAGA
CAACCGCCACAACTGTAGTACGACATCGTTGATACGACTTCAGCAAATATTTTAACA
TCACTGTGGTTGTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAG
AGTTGTACTGATATCAGCTCTGCCCTGTGAAGTAAAGCTGATG (SEQ ID NO:55)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIWGLVPHILTPQHILQSLTSRLHSDSSDQ
KGGMNAWTGAGAQICIWKVCPPPPWR (SEQ ID NO:56)

Toxin Sequence:
Leu-His-Ser-Asp-Ser-Ser-Asp-Gln-Lys-Gly-Gly-Met-Asn-Ala-Xaa4-Thr-Gly-Ala-Gly-Ala-Gln-
Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Xaa3-Xaa3-Xaa4-Arg-^ (SEQ ID NO:57)

Name: A14.3

Species: aurisiacus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGTAAATTGAACGACGTAATTTGGGGTTTGGTGCCACACATCTTAAC
CCCACAGCATATCTTGCAAAGCCTGACTTCCCGTCTTCATTCTGACAGCAGTGATCA
GAAAGGAGCACAAATATGCATCTGGAAGGTATGTCCACCACCCCCATGGAGATGAA
CACAAGGAAAAAGATGAATGACGTCAGACAACCGCCACAACTGTAGTACGACATC
GTTGATACGACTTCAGCAAATATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTG
CTTTAAAAGATTGGATTTTTCCTTGTTTAGGAGTTGTATTGATATCAGCTCTGCCCTG
TGAAATAAAGCTGATG (SEQ ID NO:58)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIWGLVPHILTPQHILQSLTSRLHSDSSDQ
KGAQICIWKVCPPPPWR (SEQ ID NO:59)

Toxin Sequence:
Leu-His-Ser-Asp-Ser-Ser-Asp-Gln-Lys-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Xaa3-Xaa3-Xaa4-Arg-^ (SEQ ID NO:60)

Name: A14.4
Species: aurisiacus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTTTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGCCACACATCTTAAC
CCCACAGCATATCTTGCAAAGCCTGACTTCCCGTCTTCGTTCTGACAGCAGTGATCA
GAAAGGAGGCATGAACGCATCGACAGGAGCAGGAGCACAAATATGCATCTGGAAG
GTATGTCCACCATCCCCATGGAGACGAACACAAGGAAAAAGATGAATGACGTCAGA
CAACCGCCACAACTGTAGTACGACATCGTTGATACGACTTCAGCAAATATTTTAACA
TCACTGTGGTTGTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAG
AGTTGTACTGATATCAGCTCTGCACTGTGAAATAAAGCTGATG (SEQ ID NO:61)

Translation:
MQTAYWVMVMMMVWITAPLFEGGKLNDVIRGLVPHILTPQHILQSLTSRLRSDSSDQK
GGMNASTGAGAQICIWKVCPPSPWRRTQGKR (SEQ ID NO:62)

Toxin Sequence:
Leu-Arg-Ser-Asp-Ser-Ser-Asp-Gln-Lys-Gly-Gly-Met-Asn-Ala-Ser-Thr-Gly-Ala-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-Arg-Thr-Gln-# (SEQ ID NO:63)

Name: Ac14.1

Species: achatinus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGCCACACATCTTAAC
CCCACAGCATATCTTGCAAAGTCTGACTTCCCGTCTTCGTTCTGACAACGGTGGTTC
GAGTGGAGCACAAATATGCATCTGGAAGGTGTGTCCACCATCCCCATGGAGACGAC
CACAAGGAAAAAGATGAACGGCGTCAGACAACCGCCACAACTGTAGTGGGACATC
GTTGATACGACTTCAGCAAATATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTG
CTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCTGCCCTA
TGAAATAAAGCTGATG (SEQ ID NO:64)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPHILTPQHILQSLTSRLRSDNGGSS
GAQICIWKVCPPSPWRRPQGKR (SEQ ID NO:65)

Toxin Sequence:
Leu-Arg-Ser-Asp-Asn-Gly-Gly-Ser-Ser-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-
Xaa3-Ser-Xaa3-Xaa4-Arg-Arg-Xaa3-Gln-# (SEQ ID NO:66)

Name: P14.2
Species: purpurascens
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGACGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGAAAACTGAACGATGTAATTCGGGGTTTGGTGCCAGACGACTTAG
CCCTACAGCTTATCTTGCAAAGTCCGGTTTTCCGTCGTCAATCTGAAGAGGAAAAAA
TATGCCTCTGGAAGATATGTCCACCACCCCCATGGAGACGATCATAAGGAAAAAAA
AATGAATGACGTCAGACAACCACCACAACTGTAATACGACATCGTTAATACGACTT
CAGCAAACATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTGCTTTAGAAGCTTG
GATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCTGCCCTATGAAATAAAGCT
GATG (SEQ ID NO:67)

Translation:
MQTAYWVMVMTMVWITAPLSEGGKLNDVIRGLVPDDLALQLILQSPVFRRQSEEEKIC
LWKICPPPPWRRS (SEQ ID NO:68)

Toxin Sequence:
Xaa2-Ser-Xaa1-Xaa1-Xaa1-Lys-Ile-Cys-Leu-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-Xaa3-Xaa3-Xaa4-
Arg-Arg-Ser-^ (SEQ ID NO:69)

Name: P14.1

Species: purpurascens
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAGGGTAGAAAACCGAACGATGTAATTCGGGGTTTGGTGCCAGATGACTTAG
CCCTACAGCTTATCTTGCAAAGTCAGGTTTCCCGTCGTGAATCTAATGGGGTGGAAA
TATGCATGTGGAAGGTATGTCCACCATCCCCATGGAGACGATCATAAGGAAAAAAA
ATGAATGACGTCAGACAACCACCACAACTGTAATACGACATCGTTAATACGACTTC
AGCAAACATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTGCTTTAAAAGATTGG
ATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCTGCCCTATGAAATAAAGCTG
ATG (SEQ ID NO:70)

Translation:
MQTAYWVMVMMMVWITAPLSEGRKPNDVIRGLVPDDLALQLILQSQVSRRESNGVEI
CMWKVCPPSPWRRS (SEQ ID NO:71)

Toxin Sequence:
Xaa1-Ser-Asn-Gly-Val-Xaa1-Ile-Cys-Met-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-
Arg-Ser-^ (SEQ ID NO:72)

Name: Sm14.1
Species: stercusmuscarum
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGTAAATTGACCGACGTAATTCGGGGTTTGGTGCCACACATCTTAAC
CCCACAGCATATCTTGCAAAGTATGACTTCCCGTCTTGGTATTGGCAGCAGTGATCA
AAATGCACAAATATGCATCTGGAAGGTATGTCCACCATCCCCATAGAGACGACCAT
AAGGAAAAAGATGAATGACGTCAGACAACCGCCACAACTGTAGTACGACATCGTTG
ATACGACTTCAGCAAATATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTGCTTT
AAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCTGCCCTGTGA
AATAAAGCTGATG (SEQ ID NO:73)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLTDVIRGLVPHILTPQHILQSMTSRLGIGSSDQN
AQICIWKVCPPSP (SEQ ID NO:74)

Toxin Sequence:
Leu-Gly-Ile-Gly-Ser-Ser-Asp-Gln-Asn-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-
Xaa3-^ (SEQ ID NO:75)

Name: Ba14.1
Species: baileyi

Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATAATGGTGTGGATTACAGTCCCTCTG
TCTGAAGGTGGTAAATTGAACGACATAATTCGGGGTTTGTTGCCAGACAACTTCCCC
CCACAGCTTACCTTGCATCGTCTGGTTTCCCGTCGTCATTCTGACAGCATTATTCTGA
GGGGCTTATGTATCTGGAAGGTGTGTGAACCTCCGCCACAAAGATGATCTGGTCCA
AAGCCAAAAAACGAATGATGTCAGACAACCGCCACAGCTTTAGTACGACATGGTTA
ATACGACTTCAGCAAATATTTCAACATCACTGTGGTTGTGAAGAAATCAGTTACTTT
AAAAGATTGGAATGATGTCAGCTGTGCACTATCAAATAAAGTTGATGTGACAAAAA
AAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAG (SEQ ID NO:76)

Translation:
MQTAYWVMVMIMVWITVPLSEGGKLNDIIRGLLPDNFPPQLTLHRLVSRRHSDSIILRG
LCIWKVCEPPPQR (SEQ ID NO:77)

Toxin Sequence:
His-Ser-Asp-Ser-Ile-Ile-Leu-Arg-Gly-Leu-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa1-Xaa3-Xaa3-Xaa3-Gln-Arg-^ (SEQ ID NO:78)

Name: Bk14.1
Species: bocki
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAAGTGATAAACTGAACGACGTAATTCGGGGTTTGGTGCCAGACAACTTAA
CCCCACAGCTTATCTTGCGAAGTCTGATTTCCCGTCGTCGTTCTGACAAGGATGATC
CGGGAGGACAAGAATGTTACTGGAACGTATGTGCACCAAACCAGGGAGACCACAT
GATCTTAAGAAAAAAGATGAATGACGACAGACAACCGCCACAACTGTAATACGAC
ATCGTTAATACGACTTCAGCAAATATTTAACATCACTGTGGTTGTGAAGAAATCAG
TTGCTTTAAAAGATTGGATTTTTCCGTGTTTAAGAGCTGTACTGATATCTGCTCTGCC
CTGTGAAATAAAGCTGATG (SEQ ID NO:79)

Translation:
MQTAYWVMVMMMVWITAPLSESDKLNDVIRGLVPDNLTPQLILRSLISRRRSDKDDPG
GQECYWNVCAPNQGDHMILRKKMNDDRQPPQL (SEQ ID NO:80)

Toxin Sequence:
Arg-Ser-Asp-Lys-Asp-Asp-Xaa3-Gly-Gly-Gln-Xaa1-Cys-Xaa5-Xaa4-Asn-Val-Cys-Ala-Xaa3-Asn-Gln-Gly-Asp-His-Met-Ile-Leu-Arg-Lys-Lys-Met-Asn-Asp-Asp-Arg-Gln-Xaa3-Xaa3-Gln-Leu-^ (SEQ ID NO:81)

Name: Cd14.1
Species: chaldaeus

Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGATGGGGATGATG
ATGGTGTGGATTACAGCCCCTCTGTCTGGAGGTGGTAAACTGAACGACGTAATTCG
GGGTTTGGTGCCAGACGACTTAACCCTACAGCGTATGTTCGAAACTCCGGTTTCCCA
TCGTCTTTCTGAGGGCAGAAATTCGACGGTACACATATGTACGTGGAAGGTATGTCC
ACCTCCCCCATGGAGACGACCACATGGACAAAGATGAATGACGTCAGACAACCTCC
ACAACTGTAGTACGACATCGTTAACACGACGTCAGCTAATCTTTTAACATCACTGTG
GCTGTGAAGAACTCGGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTG
CTGATATGAACTCTGCACTACGAAATAAAGCTGATGTGACAAACAAAAAAAAGAAA
AAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:82)

Translation:
MQTAYWVMMGMMMVWITAPLSGGGKLNDVIRGLVPDDLTLQRMFETPVSHRLSEGR
NSTVHICTWKVCPPPPWRRPHGQR (SEQ ID NO:83)

Toxin Sequence:
Leu-Ser-Xaa1-Gly-Arg-Asn-Ser-Thr-Val-His-Ile-Cys-Thr-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Xaa3-
Xaa3-Xaa4-Arg-Arg-Xaa3-His-Gly-Gln-Arg-^ (SEQ ID NO:84)

Name: Cd14.2
Species: chaldaeus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGATGGGGATGATG
ATGGTGTGGATTACAGCCCCTCTGTCTGGAGGTGGTAAACTGAACGACGTAATTCG
GGGTTTGGTGCCAGACGACTTAACCCTACAGCGTATGTTCGAAACTCCGGTTTCCCA
TCGTCTTTCTGAGGGCAGAAATTCGACGGTACACATATGTATGTGGAAGGTATGTCC
ACCTCCCCCATGGAGACGACCACATGGACAAAGATGAATGACGTCAGACAACCTCC
ACAACTGTAGTACGACATCGTTAACACGACGTCAGCTAATCTTTTAACATCACTGTG
GTTGTGAAGAAATCGGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTG
CTGATATGAACTCTGCACTACGAAATAAAGCTGATGTGACAAACGGAAAAAAAAAAA
AAAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID
NO:85)

Translation:
MQTAYWVMMGMMMVWITAPLSGGGKLNDVIRGLVPDDLTLQRMFETPVSHRLSEGR
NSTVHICMWKVCPPPPWRRPHGQR (SEQ ID NO:86)

Toxin Sequence:
Leu-Ser-Xaa1-Gly-Arg-Asn-Ser-Thr-Val-His-Ile-Cys-Met-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-
Xaa3-Xaa3-Xaa4-Arg-Arg-Xaa3-His-Gly-Gln-Arg-^ (SEQ ID NO:87)

Name: Ci14.1
Species: cinereus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGTTGG
TGTGGATTACAGCCCCTCTGCCTGAGGGTGGTAAACCGAAGCACGTAATTCGGGGT
TTGGTACCAGACGACTTAACCCCACAGCATATCTTGCGAAGTTTGATTTCCCGTCGT
TCATCTGGCTGCAGTGTTTCGTTGGGCTTCAAATGCTTCTGGAAGAGCTGTACAGTA
ATCCCAGTGAGACCATTTGTATCTCTGGAAGAAGAAAATGAATGCCAGAAAGTCCA
AATAAGTGCAGTATGGGGTCCTTGATACGACTTCAGCAAGGATCACTGTGGTTGTG
AAGAAATCAGTTGCTTTAAAAGATTTGATTTTTCCTTGTTTAAGAGTTGTACTGATAT
CAGCTCTGTACTATGAAATAAAGCTGATGTGACAAACAAAAAAAAAAAAAAAAAA
AGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:88)

Translation:
MQTAYWVMVMMLVWITAPLPEGGKPKHVIRGLVPDDLTPQHILRSLISRRSSGCSVSLG
FKCFWKSCTVIPVRPFVSLEEENECQKVQISAVWGP (SEQ ID NO:89)

Toxin Sequence:
Ser-Ser-Gly-Cys-Ser-Val-Ser-Leu-Gly-Phe-Lys-Cys-Phe-Xaa4-Lys-Ser-Cys-Thr-Val-Ile-Xaa3-Val-Arg-Xaa3-Phe-Val-Ser-Leu-Xaa1-Xaa1-Xaa1-Asn-Xaa1-Cys-Gln-Lys-Val-Gln-Ile-Ser-Ala-Val-Xaa4-Gly-Xaa3-^ (SEQ ID NO:90)

Name: Ci14.2
Species: cinereus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGGTG
GTGGTGTGGATTACAGCCCCTCTGCCTGAAGGTGGTAAACCGGAGCACGTAATTCG
GGGTTTGGTGCCAGACGACTTAACCCCACAGCTTATCTTGCGAAGTCTGATTTCCCG
TCGTAGTTCTGACGGCAAGGCAAAAAGAAATTGTTTCTGGAAGGCATGTGTACCAG
AACAATGGAGACAACGTGATCTTAAGGAAAAAGATGAATGATGTCAGACAACCGC
CATCACTGTAGTATGACATCGTTAATACGACTTAAGCAAATATTTTAACATCACTGT
GGATCTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTCGTTTAAGAGTTGT
ACTGATGTCAGCTCTGCACTGTGAAATAAAGCTGATGTGACAAACGAAAAAAAAAA
AAAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:91)

Translation:
MQTAYWVMVMMVVVWITAPLPEGGKPEHVIRGLVPDDLTPQLILRSLISRRSSDGKAK
RNCFWKACVPEQWRQRDLKEKDE (SEQ ID NO:92)

Toxin Sequence:

Ser-Ser-Asp-Gly-Lys-Ala-Lys-Arg-Asn-Cys-Phe-Xaa4-Lys-Ala-Cys-Val-Xaa3-Xaa1-Gln-Xaa4-Arg-Gln-Arg-Asp-Leu-Lys-Xaa1-Lys-Asp-Xaa1-^(SEQ ID NO:93)

Name: Ci14.3
Species: cinereus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGGTGTGGATTACAGCCCCTCTGCCTGAAGGTGGTAAACCGAAGCACGTAATTCG
GGGTTTGGTGCCAGACGACTTAACCCCACAGCTTATCTTGCGAAGTCTGATTTCCCG
TCGTAGTTCTGACGGCAAGGCAAAAAGAAATTGTTTCTGGAAGGCATGTGTACCAG
AACAATGGAGACAACGTGATCCTAAGGAAAAAGATGAATGATGTCAGACAACCGC
CATCACTGTAGTATGACATCGTTAATACGACTTAAGCAAATATTTTAACATCACTGT
GGATCTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTCGTTTAAGAGTTGT
ACTGATGTCAGCTCTGCACTGTGAAATAAAGCTGACGTGACAAGCAAAAAAAAAAA
AAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:94)

Translation:
MQTAYWVMVMMMVVWITAPLPEGGKPKHVIRGLVPDDLTPQLILRSLISRRSSDGKAK
RNCFWKACVPEQWRQRDPKEKDE (SEQ ID NO:95)

Toxin Sequence:
Ser-Ser-Asp-Gly-Lys-Ala-Lys-Arg-Asn-Cys-Phe-Xaa4-Lys-Ala-Cys-Val-Xaa3-Xaa1-Gln-Xaa4-Arg-Gln-Arg-Asp-Xaa3-Lys-Xaa1-Lys-Asp-Xaa1-^ (SEQ ID NO:96)

Name: Ci14.4
Species: cinereus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATAATGATG
GTGTGGATTACAGCCCCTCTGTCTGAAGGTGGTAAACCGAAGCACGTAATTCGGGG
TTTGGTGCCAGTCGACTTAACCCCACAGCTTATCTTGCGAAGTCTGATTTCCCGTCGT
AGTTCTGACGGCAAGGCAAAAAAACAATGTGCCTGGAAGACATGTGTACCAACCCA
ATGGAGACGACGTGATCTTAAGGAAAAAGATGAATGATGTCAGACAACCGCCATCA
CTGTAGTATGACATCGTTAATACGACTTAAGCAAATATTTTAACATCACTGTGGTTC
TGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTGA
TATCAGCTCTGCACTGTGAAATAAAGCTGATGTGACAAACAAAAAAAAAAAAAAAA
AAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:97)

Translation:
MQTAYWVMVIMMVWITAPLSEGGKPKHVIRGLVPVDLTPQLILRSLISRRSSDGKAKK
QCAWKTCVPTQWRRRDLKEKDE (SEQ ID NO:98)

Toxin Sequence:
Ser-Ser-Asp-Gly-Lys-Ala-Lys-Lys-Gln-Cys-Ala-Xaa4-Lys-Thr-Cys-Val-Xaa3-Thr-Gln-Xaa4-Arg-Arg-Arg-Asp-Leu-Lys-Xaa1-Lys-Asp-Xaa1-^ (SEQ ID NO:99)

Name: Cr14.2
Species: circumcisus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTACAGCCCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGT
TTGGTGCCACACATCTTAACCCCACAGCATATCTTGCAAGGTCTGACTTCCCGTCTT
CGTTCTGACAGCAGTGGTCAGAAAGGAGCACAAATATGCATCTGGAAGGTATGTCC
ACTATCCCCATGGAGACGACCACAAGGAAAAGATGAATGACGTCAGACAACCGCTA
CAACTGTAGTACGACATCGTTGATACGACTTCAGCAAATATTTTAACATCACTGTGG
TTGTGAAGAAATCAGCTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACT
GATATCAGCTCTGCACTATGAAATAAAGCTGATGTGACAAACAAAAAAAAAAAAAA
AAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:100)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPHILTPQHILQGLTSRLRSDSSGQK
GAQICIWKVCPLSPWRRPQGKDE (SEQ ID NO:101)

Toxin Sequence:
Leu-Arg-Ser-Asp-Ser-Ser-Gly-Gln-Lys-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Leu-Ser-Xaa3-Xaa4-Arg-Arg-Xaa3-Gln-Gly-Lys-Asp-Xaa1-^ (SEQ ID NO:102)

Name: Cn14.4
Species: consors
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTACAGCCCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGT
TTGGTGCCACACTTCTTAACCCCACAGCATATCTTGCAAAGTCTGACTTCCCGTAAT
GGTTCTGGCAGCAGTAATCAGAAAGAAGCACAACTATGCATCTGGAAGGTATGTCC
ACCAACCCCATGGAGATGACCACAAGGAAAAAGATGAACGGCGTCAGACAACCGC
CACAACTGTAGTGGGACATCGTTGATACGACTTCAGCAAATATTTTAACATCACTGT
GGTTGTGAAGAAATCAGTTGTTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGT
ACTGATATCAGCTCTGCACTATGAAATAAAGCTGATGTGACAAGCAAAAAAAAAAA
AAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:103)

Translation:

MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPHFLTPQHILQSLTSRNGSGSSNQ KEAQLCIWKVCPPTPWR (SEQ ID NO:104)

Toxin Sequence:

Asn-Gly-Ser-Gly-Ser-Ser-Asn-Gln-Lys-Xaa1-Ala-Gln-Leu-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Thr-Xaa3-Xaa4-Arg-^ (SEQ ID NO:105)

Name: Cn14.5
Species: consors
Cloned: Yes

DNA Sequence:

GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG GTGTGGATTACAGCCCCTCTGTCTGAAGGTGGTAAACTGAACGGCGTAATTCGGGG TTTGGTGTCACACATCTTAATCCCACAGCATACCTTGCGAAGTCTGACTTCCCGTGA TCGTTCTGACAACGGTGGTTCGAGTGGAGCACAAATATGCATCTGGAAGGTATGTC CACCATCCCCATGGAAATGACCACAAGGAAAAAGATGAACGGCGTCAGACAACCA CCACAACTGTAGTGGGACATCGTTGATACGACTTCAGCAAATATTTTAACATCACTG TGGTCGTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTG TACTGATATCAGCTCTGCACTATGAAATAAAGCTGATGTGACAAACAAAAAAAAAAA AAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:106)

Translation:

MQTAYWVMVMMMVWITAPLSEGGKLNGVIRGLVSHILIPQHTLRSLTSRDRSDNGGSS GAQICIWKVCPPSPWK (SEQ ID NO:107)

Toxin Sequence:

Asp-Arg-Ser-Asp-Asn-Gly-Gly-Ser-Ser-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Lys-^ (SEQ ID NO:108)

Name: Ct14.1
Species: coronatus
Cloned: Yes

DNA Sequence:

ATGCAGACGGCCTACTGGGTGATGATGATGATGATGATGGTGTGGATTACAGCCCC TCTGTCTGAAGGTGGTAAACTGAACGACGTAATTCGGGGTTTGGTGCCAGACGACTT AACCCTACAGCGTATGTTCAAAGCTCTGGTTTCCCATCGTCTTTCTGACGGCAGAGA TTGGACGGGATACATATGTATCTGGAAGGCATGTCCACGTCCCCCATGGATCCCACC AAAGGGAAAAAAGATGAATGACGTCAGACAACCGCCACAACTGTAGTACGACATCG TTAACACAACTTCAGCTAATATTTTAACATCACTGTGGTTGTGAAGAAATCGGTTGC TTTAAAAGATTGAATTTTTCGTTTAAGAGTTGTGCTGATACGAGCTCTGCACTATGA AATAAAGCTGATGTGACAAACAAAAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTT ACTCGAG (SEQ ID NO:109)

Translation:
MQTAYWVMMMMMMVWITAPLSEGGKLNDVIRGLVPDDLTLQRMFKALVSHRLSDG
RDWTGYICIWKACPRPPWIPPKGKR (SEQ ID NO:110)

Toxin Sequence:
Leu-Ser-Asp-Gly-Arg-Asp-Xaa4-Thr-Gly-Xaa5-Ile-Cys-Ile-Xaa4-Lys-Ala-Cys-Xaa3-Arg-Xaa3-Xaa3-Xaa4-Ile-Xaa3-Xaa3-Lys-# (SEQ ID NO:111)

Name: Eb14.1
Species: ebraeus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGATGATGATGATG
ATGGTGTGGATTACAGCCCCTCTGTCTGAAGGCGGTAAACTGAACGACGTAATTCG
GGGTTTGGTGCCAGACGACTTAACCCTACAGCGTATGTTCAAAAGTCTGTTTTCCCA
TCGTCTTTCTGGCGGCACATATTCGAGGGTAGACACATGCATCTGGAAGGTATGTCC
ACAATCTCCATAGGGACGATCATATGGAAAAAGATGAGTGACATCAGACAACTGCC
ACAACTGTAGTACGACATCGTTAACACGACTTCAGCTAATATTTTAACATCACTGTG
GTTGTGAAGAAATCGGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTG
CTGATATGAGCTCTGCACTATGAAATAAAGCTGATGTGACAAACAAAAAAAAAAAA
AAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:112)

Translation:
MQTAYWVMMMMMMVWITAPLSEGGKLNDVIRGLVPDDLTLQRMFKSLFSHRLSGGT
YSRVDTCIWKVCPQSP (SEQ ID NO:113)

Toxin Sequence:
Leu-Ser-Gly-Gly-Thr-Xaa5-Ser-Arg-Val-Asp-Thr-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Gln-Ser-Xaa3-^ (SEQ ID NO:114)

Name: G14.2
Species: geographus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGCTGATGATGATGG
TGTGCATCACAGCCCCTCTGCCTGAAGGTGGTAAACCGAACAGCGGAATTCGGGGT
TTGGTGCCAAACGACTTAACTCCACAGCATACCTTGCGAAGTCTGATTTCCCGTCGT
CAAACTGACGTTCTTCTGGAGGCTACCCTTTTGACAACACCAGCCCCCGAGCAGAG
ATTGTTCTGCTTCTGGAAGTCATGTACGTGGAGGCCCTACCCTTGGAGACGACGTGA
TCTTAATGGAAAACGATGAATGACGCCAGACAACCGCCACAACTGTAGTACGACAT
CGTTAATACGACTTCAGCAAACATTTTAACATAACTGTGGTTGTGAAGAAATCAGTT
GCTTTAAAAGATTGGATTTTTCCTTGTTTCAGAGTTGTACTGATATGAGCTCTGCACC

ATGAAATAAAGCTGAAGTGACGAACAAAAAAAAAAAAAAAAAAAAAGTACTCTGC
GTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:115)

Translation:

MQTAYWVMLMMMVCITAPLPEGGKPNSGIRGLVPNDLTPQHTLRSLISRRQTDVLLEA
TLLTTPAPEQRLFCFWKSCTWRPYPWRRRDLNGKR (SEQ ID NO:116)

Toxin Sequence:

Xaa2-Thr-Asp-Val-Leu-Leu-Xaa1-Ala-Thr-Leu-Leu-Thr-Thr-Xaa3-Ala-Xaa3-Xaa1-Gln-Arg-
Leu-Phe-Cys-Phe-Xaa4-Lys-Ser-Cys-Thr-Xaa4-Arg-Xaa3-Xaa5-Xaa3-Xaa4-Arg-Arg-Arg-Asp-
Leu-Asn-# (SEQ ID NO:117)

Name: Gd14.1
Species: gladiator
Cloned: Yes

DNA Sequence:

ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGGTTACAGTCCCTCG
ATCTGAAGGTGGCACGTGGAACTACTTAATTCGGGGTTTGGTGCCAGACGACCTAA
CCCCACAGCTTACCTTGCATCGTCTGGTTACCCGTCGTCATCCTGCCAACGTTAGAC
AGCAGGGGAAAATATGTGTATGGAAGGTGTGTCCACCATGGCCAGTAAGATCACCT
GGTCCACAGCCAAAAAACAAATGACGTCAGACAACCGCCACAACTTTAGTACGACA
TCGTTGATACAACTTCAGCAAGTATTTTAACATCACTGTGGCTCTGAAGAAATCAGT
TGCTTTAAAAGATTGGATTTTTCCTTGTTTTAGAGTTTTACTGATATCAGCTCTGCAC
TATGAAATAAAGATGTGACGAAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTAC
TCGAG (SEQ ID NO:118)

Translation:

MQTAYWVMVMMMVWVTVPRSEGGTWNYLIRGLVPDDLTPQLTLHRLVTRRHPANV
RQQGKICVWKVCPPWPVRSPGPQPKNK (SEQ ID NO:119)

Toxin Sequence:

His-Xaa3-Ala-Asn-Val-Arg-Gln-Gln-Gly-Lys-Ile-Cys-Val-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-
Xaa4-Xaa3-Val-Arg-Ser-Xaa3-Gly-Xaa3-Gln-Xaa3-Lys-Asn-Lys-^ (SEQ ID NO:120)

Name: Gd14.2
Species: gladiator
Cloned: Yes

DNA Sequence:

ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGGTTACAGTCCCTCG
ATCTGAAGGTGGCACGTGGAACTACTTAATTCGGGGTTTGGTGCCAGACGACCTAA
CCCCACAGCTTACCTTGCATCGTCTGGTTACCCGTCGTCATCCTGCCAACGTTAGAC
AGCAGGGGAAAATATGTGTATGGAAGGTGTGTCCACCATCGCCAGTAAGATCACCT
GGTCCACTGCCAAAAAACAAATGACGTCAGACAACCGCCACAACTTTAGTACGACA

TCGTTGATACAACTTCAGCAAGTATTTTAACATCACTGTGGCTCTGAAGAAATCAGT
TGCTTTAAAAGATTGGATTTTTCCTTGTTTTAGAGTTTTACTGATATCAGCTCTGCAC
TATGAAATAAAGATGTGACGGACAAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTT
ACTCGAG (SEQ ID NO:121)

Translation:
MQTAYWVMVMMMVWVTVPRSEGGTWNYLIRGLVPDDLTPQLTLHRLVTRRHPANV
RQQGKICVWKVCPPSPVRSPGPLPKNK (SEQ ID NO:122)

Toxin Sequence:
His-Xaa3-Ala-Asn-Val-Arg-Gln-Gln-Gly-Lys-Ile-Cys-Val-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Val-Arg-Ser-Xaa3-Gly-Xaa3-Leu-Xaa3-Lys-Asn-Lys-^ (SEQ ID NO:123)

Name: Ly14.1
Species: litoglyphus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTACAGCCCCTCTGTCTGAAGGTGATAAATTGAACGACGTAATTCGGGGT
TTGGTGCCAGATAACTTAGCCCCACAGCTTGTTTTGCAAAGTCTGGATTCCCGTCGT
CATCCTCACGGCATTCGTCAGGATGGAGCCCAAATATGTATCTGGAAGATATGTCCA
CCATCCCCATGGAGACGACTTGGATCTTAAGAAAAGAAACAATTGACGTCAGACAA
CCGCCACATCTTGAGTACGACATCGTTAATACGACTTCAGCAAATATGAAATTTTCA
GCATCACTGTGGTTGTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTGTCCTTGTT
TAAGAGTTGTACTGATGTCATCTCTGCACTATGAAATAAAGCTGATGTGAAAAAAA
AAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:124)

Translation:
MQTAYWVMVMMMVWITAPLSEGDKLNDVIRGLVPDNLAPQLVLQSLDSRRHPHGIRQ
DGAQICIWKICPPSPWRRLGS (SEQ ID NO:125)

Toxin Sequence:
His-Xaa3-His-Gly-Ile-Arg-Gln-Asp-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-Arg-Leu-Gly-Ser-^ (SEQ ID NO:126)

Name: Ly14.2
Species: litoglyphus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTACAGCCCCTCTGTCTGAAGGTGATAAATTGAACGACGTAATTCGGGGT
TTGGTGCCAGATAACTTAGCCCCACAGCTTGTTTTGCAAAGTCTGGATTCCCGTCGT

CATCCTCACGGCATTCGTCAGGATGGAGCCCAAATATGTATCTGGAAGATATGTCCA
CCATCCCCATGGAAACGACTTGGATCTTAAGAAAAGAAACAATTGACGTCAGACAA
CCGCCACAACTTGAGTACGACATCGTTAATACAACTTCAGCAAATATGAAATTTTCA
GCATCACTGTGGTTGTGAAGAAATCAGTTGCTTTAAAGGATTGGATTTGTCCTTGTT
TAAGAGTTGTACTGATGTCATCTCTGCACTATGAAATAAAGCTGATGTGACAAGCA
AAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC
(SEQ ID NO:127)

Translation:
MQTAYWVMVMMMVWITAPLSEGDKLNDVIRGLVPDNLAPQLVLQSLDSRRHPHGIRQ
DGAQICIWKICPPSPWKRLGS (SEQ ID NO:128)

Toxin Sequence:
His-Xaa3-His-Gly-Ile-Arg-Gln-Asp-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-
Ser-Xaa3-Xaa4-Lys-Arg-Leu-Gly-Ser-^ (SEQ ID NO:129)

Name: Lt14.1
Species: litteratus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGGGGATTACAGCCCCTCTGTCTGAAGGTCGTAAATTGAACGACGCAATTCGGGG
TTTGGTGCCAGATGACTTAACCCCACAGCTTTTGCGAAGTCCGGTTTCGACTCCTTA
TCCTGAGTTTCATCTTGATGAACCTTATCTGAAGATACCCGTATGTATCTGGAAGAT
ATGTCCACCAAACCTATTGAGACGACGTGATCTTAAGAAAAGAAACAAAGTACGTC
AGACAACCGCCACAACTTGAGTACGACATCGTTCATACAACTTGAGCAAATATTTC
AGCATCACTATGGTTGTGAAGAAATCAGTTGCTTTAAAAGATTGGATCTTTCCTTGT
TTAAGAGTTGTATTGATGTCAGCTCTGCACTCTGAAATAAAGCTGATGTGACAAACA
AAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC
(SEQ ID NO:130)

Translation:
MQTAYWVMVMMMVGITAPLSEGRKLNDAIRGLVPDDLTPQLLRSPVSTPYPEFHLDEP
YLKIPVCIWKICPPNLLRRRDLKKRNKVRQTTATT (SEQ ID NO:131)

Toxin Sequence:
Ser-Xaa3-Val-Ser-Thr-Xaa3-Xaa5-Xaa3-Xaa1-Phe-His-Leu-Asp-Xaa1-Xaa3-Xaa5-Leu-Lys-Ile-
Xaa3-Val-Cys-Ile-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-Asn-Leu-Leu-Arg-Arg-Arg-Asp-Leu-Lys-Lys-
Arg-Asn-Lys-Val-Arg-Gln-Thr-Thr-Ala-Thr-Thr-^ (SEQ ID NO:132)

Name: Lt14.2
Species: litteratus
Cloned: Yes

DNA Sequence:

GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGGGGATTACAGCCCCTCTGTCTGAAGGTCGTAAATTGAACGACGCAATTCGGGG
TTTGGTGCCAAATGACTTAACCCCACAGCTTTTGCAAAGTCTGGTTTCCCGTCGTCA
TCGTGTGTTTCATCTTGACAACACTTATCTCAAGATACCCATATGTGCCTGGAAGGT
ATGTCCACCAACCCCATGGAGACGACGTGATCTTAAGAAAAGAAACAAATGACGTC
AGACAACCGCCACAACTTGAGTACGACATTGTTAATGCGACTTGAGCAAATTTTTCA
GCATCACTATGGTTGTAAAGAAATCAGCTGCTTTAAACGATTGGATCTTTCCTTATT
TAAGAGTTGTATTGATGTCAGCTCTGCACTCTGAAATAAAGCTGATGTGACAAACA
AAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC
(SEQ ID NO:133)

Translation:

MQTAYWVMVMMMVGITAPLSEGRKLNDAIRGLVPNDLTPQLLQSLVSRRHRVFHLDN
TYLKIPICAWKVCPPTPWRRRDLKKRNK (SEQ ID NO:134)

Toxin Sequence:

His-Arg-Val-Phe-His-Leu-Asp-Asn-Thr-Xaa5-Leu-Lys-Ile-Xaa3-Ile-Cys-Ala-Xaa4-Lys-Val-
Cys-Xaa3-Xaa3-Thr-Xaa3-Xaa4-Arg-Arg-Arg-Asp-Leu-Lys-Lys-Arg-Asn-Lys-^ (SEQ ID
NO:135)

Name: Ls14.1
Species: loroisii
Cloned: Yes

DNA Sequence:

GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTAAAGGCCCTGTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGG
TTTGGTGCCAGACGACTTAACCCCACAGCTTATCTTGCAAAGTCTGATGTCCCGTCG
TCGTTCTGACAGCGATGTTCGGGAGGTGTACATATTATGCATCTGGAAGATATGTCC
ACCATTGCCATGAAGACGACATGATCTTAAGGAAAAGGATAAACGACGTCAGACAA
CCGCTACAACTGTAGTACGACATCGTTAATACGACTTCAGCAAATATTTGAACATCA
CTGTGGTTGTGAAGAAATCAGTTGCTTTAAACGATTGGATTTTTCCTTAAGAGTTGC
ACTGATATCAGCTCTGCACTATGAAATAAAGCTGATGTGACTACCAAAAAAAAAAAA
AAAAAAAAAGTACTNTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID
NO:136)

Translation:

MQTAYWVMVMMMVWIKGPVSEGGKLNDVIRGLVPDDLTPQLILQSLMSRRRSDSDVR
EVYILCIWKICPPLP (SEQ ID NO:137)

Toxin Sequence:

Arg-Ser-Asp-Ser-Asp-Val-Arg-Xaa1-Val-Xaa5-Ile-Leu-Cys-Ile-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-
Leu-Xaa3-^ (SEQ ID NO:138)

Name: M14.2
Species: magus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTACAGCCCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGT
TTGGTGCCACACTCCTTAACCCCACAGCATATCTTGCAAAGTCTGACTTCCCGTAAT
GGTTCTGGCAGCAGCAATCAGAAAGAAGCACAACTATGCATCTGGAAGGTATGTCC
ACCATCCCCATGGAGATGACCACAAGGAAAAAGATGAACGGCGTCAGACAACCGC
CACAACTGTAGTGGGACATCGTTGATACGACTTCAACAAATATTTTAACATCACTGT
GGTTGTAAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGT
ACTGATATCAGCTCTGCACTATGAAATAAAGCTGATGTGACAAACAAAAAAAAAAA
AAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:139)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPHSLTPQHILQSLTSRNGSGSSNQ
KEAQLCIWKVCPPSPWR (SEQ ID NO:140)

Toxin Sequence:
Asn-Gly-Ser-Gly-Ser-Ser-Asn-Gln-Lys-Xaa1-Ala-Gln-Leu-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-^ (SEQ ID NO:141)

Name: Mi14.3
Species: miles
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGATGATGGTGGTG
ATGATGGTGGGGGTTACTGTCGCTGGCTCCCTGCCTGTGTTTGATGACGACAACGAC
TCTGACCCCGCTGTCAAGCGCGCTATCACGTGGTCCCGCATCCTGGGCGTGTCTCCA
GCCTTCCTGGCACAGCAGCGAGCGCTGGTTCCCTTCGCCAACCGATTCATCAGTGAG
CAGAAACGTTTCCGACCCGCCATGCAGAGCCGATCAGGAGGAATGTCGCTGTGCCT
ATGGAAAGTGTGTCCTGCAGCCCCCTGGCTGGTCGCCAAACGTAAACAGGAAACCA
GCGACTACTGACGTCATACCTCTAAAGACCCACTCATGACGTCAACGCTGAACTGA
CGTCACCGACAGCTCCAACGTCACAGCAGGAGCGAGAGAGAGGCTGGAGCATTTCT
CTTTCTTTTGGTTTTTCGAGTTGAAGTGTGATCAGCTGGGCTGGTGAAAAAATTGTTG
AGTAAAGTTGAATGAAAATCAAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGGTA
CTCGAGGCTTAAAGGCGNAATTC (SEQ ID NO:142)

Translation:
MQTAYWVMMMVVMMVGVTVAGSLPVFDDDNDSDPAVKRAITWSRILGVSPAFLAQQ
RALVPFANRFISEQKRFRPAMQSRSGGMSLCLWKVCPAAPWLVAKRKQETSDY (SEQ ID NO:143)

Toxin Sequence:
Phe-Arg-Xaa3-Ala-Met-Gln-Ser-Arg-Ser-Gly-Gly-Met-Ser-Leu-Cys-Leu-Xaa4-Lys-Val-Cys-Xaa3-Ala-Ala-Xaa3-Xaa4-Leu-Val-Ala-Lys-Arg-Lys-Gln-Xaa1-Thr-Ser-Asp-Xaa5-^ (SEQ ID NO:144)

Name: Mi14.4
Species: miles
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGGTGGGTTCACCGTCGGGAGTCACGTCCATCGGTCTCACAGTCCTACGTCGCGCA
ACCATGGTGATGACTCCATTCATGACAAGACGATTCATCAACATCTGTTTGCCCGTC
TTCCTCTGGAGAACAACGACGACCATCGTTCTGTGGATCTTCCTGCAGTGTATGCGC
CGGGCCAGGCACGTGTGCGTTCTACTTTTGTTCTTGACCTCATTGCAGATAGGGGTT
GGTGCAGACGACATGAAACTACAGCGCCAAAGACGTCAAGGTTTCTGTTGCGTCGT
TATCCCGATTCTTTGGTTCTGTTGTGGGGGTTACCGCACAAATGGCACTGCACTGGC
CGATTGAAAGAACTGCAATAAACGGAATGGCAAGAAGGAATAAAAAAAAAAAAAAA
AAAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:145)

Translation:
MQTAYWVMVMMMVVGSPSGVTSIGLTVLRRATMVMTPFMTRRFINICLPVFLWRTTT
TIVLWIFLQCMRRARHVCVLLLFLTSLQIGVGADDMKLQRQRRQGFCCVVIPILWFCCG
GYRTNGTALAD (SEQ ID NO:146)

Toxin Sequence:
Xaa2-Gly-Phe-Cys-Cys-Val-Val-Ile-Xaa3-Ile-Leu-Xaa4-Phe-Cys-Cys-Gly-Gly-Xaa5-Arg-Thr-Asn-Gly-Thr-Ala-Leu-Ala-Asp-^ (SEQ ID NO:147)

Name: Mu14.1
Species: muriculatus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTTTG
TCTGAAGGTGGTAAACTGAACGATGTAATTCGGGGTTTCGCGCTAGATGACTTAGCC
CAAAGCCGTATTATGCAAAGTCTGGTTTTCAGTCATCAGCCTCTTCCAACGGCATCC
ATATGTATCTGGAAGATATGTCCACCAGACCCATGGAGACGACATGATCTTCAGAA
AAGTAACAAATGACGTCAGACAACCGCCACAACTTGAATACAACATCATTAATACG
ACTTCAGCAAATATTTTAACATCACTGTGATTGTTCGGAAGTCAGTTGCTTTAAAGG
ATTGGATTTGTCCCTGTTGTATTGATGTCAACTCTGCACTATGAAATAAAGCTGATG
TGACAAACAAGAAAAAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAG
(SEQ ID NO:148)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGFALDDLAQSRIMQSLVFSHQPLPTAS ICIWKICPPDPWRRHDLQKSNK (SEQ ID NO:149)

Toxin Sequence:
Ile-Met-Gln-Ser-Leu-Val-Phe-Ser-His-Gln-Xaa3-Leu-Xaa3-Thr-Ala-Ser-Ile-Cys-Ile-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-Asp-Xaa3-Xaa4-Arg-Arg-His-Asp-Leu-Gln-Lys-Ser-Asn-Lys-^ (SEQ ID NO:150)

Name: Ms14.1
Species: musicus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGATGATGACGATGATGGTGTGGATGACAGCCCC
TCTGTCTGAAGGTCGTCCACTGAGCGACGAAGTTCGGGGTATGGTGCCAGGCGACT
TGGTCCTACAGTATCTGTTCCCAAGTCTGGCTTTCAGTCCTCCGGACATATGTACGT
GGAAGGTATGTCCACCACCCCCATGGAGACGACCAAAAAAAAATAACAGACGTCAG
ACAGCCGCCACAACTGTAGTACGACATCGTTGATACGGCTTCAGCAAATATTTTCAA
CATCACTGCGGTTGTGAAGAAATCAGTTGCTTTAAAATGTTGGATTTTTCCTTGTTTA
AAAGAGCTGTACTGATGTCAGCCCTGCATTACGAAATAAAGCTGATGTGACAAACA
AAAAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAG (SEQ ID NO:151)

Translation:
MQTAYWVMMMTMMVWMTAPLSEGRPLSDEVRGMVPGDLVLQYLFPSLAFSPPDICT WKVCPPPPWRRPKKITDVRQPPQL (SEQ ID NO:152)

Toxin Sequence:
Gly-Met-Val-Xaa3-Gly-Asp-Leu-Val-Leu-Gln-Xaa5-Leu-Phe-Xaa3-Ser-Leu-Ala-Phe-Ser-Xaa3-Xaa3-Asp-Ile-Cys-Thr-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Xaa3-Xaa3-Xaa4-Arg-Arg-Xaa3-Lys-Lys-Ile-Thr-Asp-Val-Arg-Gln-Xaa3-Xaa3-Gln-Leu-^ (SEQ ID NO:153)

Name: Ms14.2
Species: musicus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGATGATGATGATGATGGTGTGGATGACAGCCCC
TCTGTCTGAAGGTCGTAAACTGATCGACAAAGTTCGGGGTATGGGGCCAGGCGACT
TATCCCTACAGAAAATGTTCCCAAGTCTGGCTTTAGGTCCTGGGGGAGACGTAATAT
GTAGGTGGAAGGTATGTCCACCAACCCCATGGAAACGACTAATAAAATAACTGACG
TCAGACAGCCGCCACAACTGTAGTACGACATCGTTGATACGACTTCAGCAAATATTT
CAACATCACTGCGGTTGTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTG

TTTAAAGAGTTGTACTGATATCAGCTCTGCATTACGAAATAAAGCTGATGTGACAAA
CAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAG (SEQ ID NO:154)

Translation:

MQTAYWVMMMMMMMVWMTAPLSEGRKLIDKVRGMGPGDLSLQKMFPSLALGPGGD
VICRWKVCPPTPWKRLIK (SEQ ID NO:155)

Toxin Sequence:

Gly-Met-Gly-Xaa3-Gly-Asp-Leu-Ser-Leu-Gln-Lys-Met-Phe-Xaa3-Ser-Leu-Ala-Leu-Gly-Xaa3-
Gly-Gly-Asp-Val-Ile-Cys-Arg-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Thr-Xaa3-Xaa4-Lys-Arg-Leu-
Ile-Lys-^ (SEQ ID NO:156)

Name: Ms14.3
Species: musicus
Cloned: Yes

DNA Sequence:

ATGCAGACGGCCTACTGGGTGATGATGATGATGACGATGATGGTGTGGATGACAGC
CCCTCTGTCTGAAGGTCGTCCACTGAGCGACAAAGTTCGGGGTATGGTGCCAGGCG
ACTTAGCCCTGCAGTATCTGTTCCCAAGTCTGGCTTTCAATCCCCCGGACATATGTA
CGTGGAAGGTATGTCCACCACCCCCATGGAGACGACCAAAAAAAATAACTGACGTC
GGACAGCCGCCACAACTGTAGTACGACATCGTTGATACGACTTCAGCAAATATTTTC
AACATCACTGCGGTTGTGAAGAAATCAGTTGTTTTAAAAGGTTGGATTTTTCCTTGT
TTAAAAGAGCTGTACTGATGTCAGCTCTGCATTACGAAATAAAGCTGATGTGACAA
ACGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAG
(SEQ ID NO:157)

Translation:

MQTAYWVMMMMTMMVWMTAPLSEGRPLSDKVRGMVPGDLALQYLFPSLAFNPPDI
CTWKVCPPPPWRRPKKITDVGQPPQL (SEQ ID NO:158)

Toxin Sequence:

Gly-Met-Val-Xaa3-Gly-Asp-Leu-Ala-Leu-Gln-Xaa5-Leu-Phe-Xaa3-Ser-Leu-Ala-Phe-Asn-
Xaa3-Xaa3-Asp-Ile-Cys-Thr-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Xaa3-Xaa3-Xaa4-Arg-Arg-Xaa3-
Lys-Lys-Ile-Thr-Asp-Val-Gly-Gln-Xaa3-Xaa3-Gln-Leu-^ (SEQ ID NO:159)

Name: Ms14.4
Species: musicus
Cloned: Yes

DNA Sequence:

ATGCAGACGGCCTACTGGGTGATGATGATGACGATGATGGTGTGGATGACAGCCCC
TCTGTCTGAAGGTCGTCCACTGAGCGACAAAGTTCGGGGTATGGTGCCAGGCGACT
TAGTCCTGCAGTATCTGTTCCCAAGTCTGGCTTTCAATCCTCCGGACATATGTACGT
GGAAGGTATGTCCACCACCCCCATGGAGACGACCAAAAAAAATAACTGACGTCAGA

CAGCCGCCACAACTGTAGTACGACATCGTTGATACGACTTCAGCAAATATTTTCAAC
ATCACTGCGGTTGTGAAGAAATCAGTTGTTTTAAAAGGTTGGATTTTTCCTTGTTTAA
AAGAGCTGTACTGATGTCAGCTCTGCATTACGAAATAAAGCTGATGTGACAAGCAA
AAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAG (SEQ ID NO:160)

Translation:
MQTAYWVMMMTMMVWMTAPLSEGRPLSDKVRGMVPGDLVLQYLFPSLAFNPPDICT
WKVCPPPPWRRPKKITDVRQPPQL (SEQ ID NO:161)

Toxin Sequence:
Gly-Met-Val-Xaa3-Gly-Asp-Leu-Val-Leu-Gln-Xaa5-Leu-Phe-Xaa3-Ser-Leu-Ala-Phe-Asn-
Xaa3-Xaa3-Asp-Ile-Cys-Thr-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Xaa3-Xaa3-Xaa4-Arg-Arg-Xaa3-
Lys-Lys-Ile-Thr-Asp-Val-Arg-Gln-Xaa3-Xaa3-Gln-Leu-^ (SEQ ID NO:162)

Name: Mt14.2
Species: mustelinus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGCGTGGTATACAACCCCTGT
GTCTGAATGTGGGAAATTGAACAACGTAATTCGGGGTTTTGTGCCAAAGGACTGGA
CCCCAATGCTTCCCTGGCGTCGTCTAGTTTCCCATACCAGCAGCAAGTATCCAGGTG
TGACTTTTTGTCCATGGAAGGTGTGTCCGCCAGCGCCATGGAGAATACTTGGGGTCT
AACGCAAAAAAATACATGACGTCAGACAACCGCCACCGCTTTAGTACGACATCGTT
CATACGTCTCCAGCAAGTATTTTAACATCACTGTGGTTGTGAAGAAGTCAGTAGCTT
TAAAAGATTGGATTTTTTCCTTGTTTAAGAGTTGTACTGACATGAGTTCTGCACTATG
AAATAAAGTTGATGTGACGAACGAAAAAAAAAAAAAAAAAAAAGTACTCTGCGTT
GTTACTCGAG(SEQ ID NO:163)

Translation:
MQTAYWVMVMMMAWYTTPVSECGKLNNVIRGFVPKDWTPMLPWRRLVSHTSSKYP
GVTFCPWKVCPPAPWRILGV (SEQ ID NO:164)

Toxin Sequence:
Leu-Val-Ser-His-Thr-Ser-Ser-Lys-Xaa5-Xaa3-Gly-Val-Thr-Phe-Cys-Xaa3-Xaa4-Lys-Val-Cys-
Xaa3-Xaa3-Ala-Xaa3-Xaa4-Arg-Ile-Leu-Gly-Val-^ (SEQ ID NO:165)

Name: Nb14.1
Species: nobilis
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGATGATGGTGGTG
GTGATGATGGTGGGGGTTACTGTCGCTGGCTCACTGTCTGTGTTTGATGATGACAAC
GACTCTGACCCAGCTGTCAAGCGCGCCATCACGTGGTCTCGATTCCTGGGCGCGTCT

CCAGCCTTCCTGGCACAGCAGCGAGCGCTGGCTCCCTTCGCCAACCGACCCATCAAT
GAGCAGAAACGTTTCCGACCTGCCGTGAAGAGCCGATCACGACGAGCGCCGCCGTG
CGTGTGGAAGGTGTGTCCCGCTCCCCCCTGGCTGGTCACCAAACGTAAACAGGAAA
CCAGCGACTACTGACGTCATACCTCAATAGACCGACTCATGACTTCAACGCTGAATT
GACGTCACCGAGAGCTCCAACGTCACAGCAGGAGCGAGAGAGAGAGAGAGAGAGA
GAGAAAGAGAGAGAGAAAGGCTGGAGTATTTCTCTTTCTTTTGGTTTTTCGTGTTGA
AGTGTGATCAGCTGGGCTGGTTCAAAATTGTTGAATAAAGTTGAATGAAAATCAAA
AAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC
(SEQ ID NO:166)

Translation:
MQTAYWVMMMVVVMMVGVTVAGSLSVFDDDNDSDPAVKRAITWSRFLGASPAFLA
QQRALAPFANRPINEQKRFRPAVKSRSRRAPPCVWKVCPAPPWLVTKRKQETSDY
(SEQ ID NO:167)

Toxin Sequence:
Phe-Arg-Xaa3-Ala-Val-Lys-Ser-Arg-Ser-Arg-Arg-Ala-Xaa3-Xaa3-Cys-Val-Xaa4-Lys-Val-Cys-Xaa3-Ala-Xaa3-Xaa3-Xaa4-Leu-Val-Thr-Lys-Arg-Lys-Gln-Xaa1-Thr-Ser-Asp-Xaa5-^ (SEQ ID NO:168)

Name: Nb14.2
Species: nobilis
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTACAGCCCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGT
TTGGTGCCACACTTCTTAACCCCACAGCATATCTTGCAAAGTCTGACTTCCCGTAAT
GGTTCTGGCAGCAGTAATCAGAAAGAAGCGCAACTATGCATCTGGAAGGTATGTCC
ACCAACCCCATGGAGATGATCACAAGGAAAAAGATGAACGGCGTCAGACAACCGC
CACAACTGTAGTGGGACATCGTTGATACGACTTCAGCAAATATTTTAACATCACTGT
GGTTGTGAAGAAATCAGTTGTTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGT
ACTGATATCAGCTCTGCACTATGAAATAAAGCTGATGTGACAAGCAAAAAAAAAAA
AAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:169)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPHFLTPQHILQSLTSRNGSGSSNQ
KEAQLCIWKVCPPTPWR (SEQ ID NO:170)

Toxin Sequence:
Asn-Gly-Ser-Gly-Ser-Ser-Asn-Gln-Lys-Xaa1-Ala-Gln-Leu-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Thr-Xaa3-Xaa4-Arg-^ (SEQ ID NO:171)

Name: Nb14.3
Species: nobilis

Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGATGATGGTGGTG
GTGATGATGGTGGGGGTTACTGTCGCTGGCTCACTGTCTGTGTTTGATGACGACAAT
GACTCTGACCCAGCTGTCAAGCGCGCCATCACGTGGTCTCGATTCCTGGGCGCGTCT
CCAGCCTTCCTGGCACAGCAGCGAGCGCTGGCTCCCTTCGCCAACCGACCCATCAAT
GAGCAGAAACGTTTCCGACCTGCCGTGAAGAGCCGATCACGACGAGCGCCGCCGTG
CGTATGGAAGGTGTGTCCCGCTCCCCCCTGGCTGGTCACCAAACGTAAACAGGAAA
CCAGCGACTACTGACGTCATACCTCAATAGACCGACTCATGACTTCAACGCTGAATT
GACCTCACCGAGAGCTCCAACGTCACAGCAGGAGCGAGAGAGAGAGAGAGAGAGA
GAGAGAGAGAAAGGCTGGAGTATTTCTCTTTCTTTCGGTTTTTCGTGTTGAAGTGTG
ATCAGCTGGGCTGGTTCAAAATTGTTGAATAAAGTTGAATAAAAAAAAAAAAAAAA
AAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:172)

Translation:
MQTAYWVMMMVVVMMVGVTVAGSLSVFDDDNDSDPAVKRAITWSRFLGASPAFLA
QQRALAPFANRPINEQKRFRPAVKSRSRRAPPCVWKVCPAPPWLVTKRKQETSDY
(SEQ ID NO:173)

Toxin Sequence:
Phe-Arg-Xaa3-Ala-Val-Lys-Ser-Arg-Ser-Arg-Arg-Ala-Xaa3-Xaa3-Cys-Val-Xaa4-Lys-Val-Cys-Xaa3-Ala-Xaa3-Xaa3-Xaa4-Leu-Val-Thr-Lys-Arg-Lys-Gln-Xaa1-Thr-Ser-Asp-Xaa5-^ (SEQ ID NO:174)

Name: Pr14.1
Species: parius
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGGTGTGGATTACAGCCCCTTTGTCTGAAGGTGGTAAACCGAAGCACGCAATTCG
GGGTTTGGTGCCAGACGACTTAACCCCACAGCTTATCTTGCGAAGTCTGATTTCCCG
TCGTAGTTCTTTCGGCAAGGATGCGAAACCCCCCTTTAGTTGTTCAGGCCTCCGAGG
GGGTTGCGTCCTACCTCCCAATCTCAGGCCAAAGTTCAACAAAGGTGGATAACAAA
CCCAAGCGTTCCTAGTTATACGAATGCCAGCAAATAAAAGCAGTTTGATTGTGAAA
AAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC
(SEQ ID NO:175)

Translation:
MQTAYWVMVMMMVVWITAPLSEGGKPKHAIRGLVPDDLTPQLILRSLISRRSSFGKDA
KPPFSCSGLRGGCVLPPNLRPKFNKGG (SEQ ID NO:176)

Toxin Sequence:
Xaa3-Xaa3-Phe-Ser-Cys-Ser-Gly-Leu-Arg-Gly-Gly-Cys-Val-Leu-Xaa3-Xaa3-Asn-Leu-Arg-Xaa3-Lys-Phe-Asn-Lys-Gly-# (SEQ ID NO:177)

Name: Pr14.2
Species: parius
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGT
GATGTGGATTACAGCCCCTCTGTCTGAAGGTGGTAAACCGAAGCTCATAATTCGGG
GTTTGGTGCCAAACGACTTAACCCCACAGCGTATCTTGCGAAGTCTGATTTCCGGGC
GTACTTATGGCATCTATGATGCGAAACCCCCCTTTAGTTGTGCAGGCCTCCGAGGGG
GTTGCGTCCTACCTCCCAATCTCAGGCCAAAGTTCAAGGAAGGTCGATAAAAAACC
CAAGCGTTCCTAGTTATACGAATGCCAGCAAATAAAAGCAGTTTGATTGCGAAAAA
AAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:178)

Translation:
MQTAYWVMVMMMVMWITAPLSEGGKPKLIIRGLVPNDLTPQRILRSLISGRTYGIYDA
KPPFSCAGLRGGCVLPPNLRPKFKEGR (SEQ ID NO:179)

Toxin Sequence:
Xaa3-Xaa3-Phe-Ser-Cys-Ala-Gly-Leu-Arg-Gly-Gly-Cys-Val-Leu-Xaa3-Xaa3-Asn-Leu-Arg-Xaa3-Lys-Phe-Lys-Xaa1-# (SEQ ID NO:180)

Name: Pl14.1
Species: planorbis
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGATGATGATGATG
GTGTGGATTACAGGCCATCTGTCTGAAGGTGGCAAATTGAAGGATGCAATTAGGGG
TTTGGTGCCAGACGACTTGACCTCAATGTTTGCGTTGCATCTTCCGGTTTCCCATTCT
CGGTCTAGCAGCAATGGTCTGAAGAGAGCTGACCTATGTATCCACAAGATTTGTCC
ACCACGGTATCACCAAAGCCAACAATAAAAGACGTCAGACAACCACCACAACTTTA
GTATGACATCGTTAATAGGACTTCAGCAAGTATTTTAACATCACTGTGGTTGTGATG
AAATCAGTCGCCTTAAAAGATTGGCTTTTTCCTTGTTTAAGAGTTGTACTTGTATCAG
CTTTGCACTTCGAAATAAAGTTGATGTGATGAACCAAAAAAAAAAAAAAAAAAAAG
TACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:181)

Translation:
MQTAYWVMMMMMVWITGHLSEGGKLKDAIRGLVPDDLTSMFALHLPVSHSRSSSNG
LKRADLCIHKICPPRYHQSQQ (SEQ ID NO:182)

Toxin Sequence:
Ser-Ser-Ser-Asn-Gly-Leu-Lys-Arg-Ala-Asp-Leu-Cys-Ile-His-Lys-Ile-Cys-Xaa3-Xaa3-Arg-Xaa5-His-Gln-Ser-Gln-Gln-^ (SEQ ID NO:183)

Name: Pu14.1
Species: pulicarius
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGATGGTGTGGGTTACAGCGCC
TGTGTCTGAAGGTGGTAAATTGAGCGACGTAATTCGGGGTTTGGTGCCAGACGACA
TAACCCCACAGATTATTTTGCAAAGTCTGAATGCCAGTCGTCATGCTTACAGACGTG
TTCGTCTGAGAGGACAGATATGTATCTGGAAGGTATGTCCACCACTACTACAATGG
ATACATCCATTAGTAAAAAGATGAATGACATCAGACAACCGCCACAACTGTAGTAC
GACATCGTTAACACGACTTCAGCAAATATTCTAACATCACAGTGGGTTGTGAAGAN
ATCGGGTTGGCTTTAAAAAAAANAATGGGGGNTTTTCCCCNTGGGTTTAAAAAAAN
NTNGGNNCCGGGNAANNNCCCNNNNTNNNCCCCCCCCNNTNGGGAGAAAAAAAAA
ANNCCNNTNNNGGGGGGNNNNCNAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAN
CCCCNGGGGGGNTGNTTTNNCCCCCCNCCCCNGGGGGGGGGGGGNGNTTTNNCCCCC
CCCCCGNGGGGGGGGGGGNTTTTNNTTTNNGGGGGNGCCCCCCCCCCCCCCNNNCN
NNNNAANAANNNNNGGGGGGGGGGAANAAAAANANNNNNNNNNNNNNNNNNTT
TTNTCNNTCNNCCGNGNNGNNAAAAAAAAAANTTNATTTNTNNANNNCNNCNNNCC
NNCNNCNNACCCNNCCCCNNCCNCNNCANNCNNAGANNANGAGGGGGGGGNGNN
NNGGNGNANNNNNANNNNNNNGAANNNGAGGNGNGNNNCNCGNCNNCGCNCNNG
NC (SEQ ID NO:184)

Translation:
MQTAYWVMVMMMMVWVTAPVSEGGKLSDVIRGLVPDDITPQIILQSLNASRHAYRRV
RLRGQICIWKVCPPLLQWIHPLVKR (SEQ ID NO:185)

Toxin Sequence:
Val-Arg-Leu-Arg-Gly-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Leu-Leu-Gln-Xaa4-Ile-His-Xaa3-Leu-Val-Lys-Arg-^ (SEQ ID NO:186)

Name: Pu14.2
Species: pulicarius
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGATGGTGTGGGTTACAGCGCC
TGTGTCTGAAGGTGGTAAATTGAGCGACGTAATTCGGGGTTTGGTGCCAGACGACTT
AACCCCACAGATTATCTTGCAAAGTCTGAATGCCAGTCGTCATGCTTACAGACGTGT
TCGTCCGAGAGGACAGATATGTATCTGGAAGGTATGTCCACCACTACTACAATGGA
TACATCCATTAGTAAAAAGATGAATGACATCAGACAACCGCCACAACTGTAGTACG
GCATCGTTAACACGACTTCAGCAAATATTTTAACATCACAGTGGTTGTGAAGAAATC
GGTTGCTTTAAAAAAAGATTGGGTTTTTCCTTGTTTAAGAGTTGTACTGATATCAGTT
CTGCACTATGAAATAAAGCTGATGTGACGAACAAAAAAAAAAAAAAAAAAAGTA
CTCTGCGTTGTTACTCGAG (SEQ ID NO:187)

Translation:
MQTAYWVMVMMMMVWVTAPVSEGGKLSDVIRGLVPDDLTPQIILQSLNASRHAYRR
VRPRGQICIWKVCPPLLQWIHPLVKR (SEQ ID NO:188)

Toxin Sequence:
Val-Arg-Xaa3-Arg-Gly-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Leu-Leu-Gln-Xaa4-Ile-His-Xaa3-Leu-Val-Lys-Arg-^ (SEQ ID NO:189)

Name: Pu14.3
Species: pulicarius
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGATGGTGTGGGTTACAGCGCC
TGTGTCTGAAGGTGGTAAATTGAGCGACGTAATTCGGGGTTTGGTGCCAGACGACA
TAACCCCACAGATTATCTTGCAAAGTCTGAATGCCAGTCGTCATGCTTACAGACCTG
TTCGTCTGAGAGGACAGATATGTATCTGGAAGGTATGTCCACCACTACTACAATGG
ATACATCCATTAGTAAAAAGATGAATGACATCAGACAACCGCCACAACTGTAGTAC
GACATCGTTAACACGACTTCAGCAAATATTTTAACATCACAGTGGTTGTGAAGAAAT
CGGTTGCTTTAAAAAAAGATTGGGTTTTTCCTTGTTTAAGAGTTGTACTGATATCAGT
TCTGCACTATGAAATAAAGCTGATGTGACGAACAAAAAAAAAAAAAAAAAAAGT
ACTCTGCGTTGTTACTCGAG (SEQ ID NO:190)

Translation:
MQTAYWVMVMMMMVWVTAPVSEGGKLSDVIRGLVPDDITPQIILQSLNASRHAYRPV
RLRGQICIWKVCPPLLQWIHPLVKR (SEQ ID NO:191)

Toxin Sequence:
Xaa3-Val-Arg-Leu-Arg-Gly-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Leu-Leu-Gln-Xaa4-Ile-His-Xaa3-Leu-Val-Lys-Arg-^ (SEQ ID NO:192)

Name: Ra14.1
Species: rattus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGGTGGTGGTGGGGTTCACCGTCGG
GGGTCACGTCCATCAATCTCACAGTCCTACATCGCGCAGCCATGGTGATGACTCCAT
TCATGACAAGACGATTCATCAACATCTGTTTGCCCGTCTTCCTCTGGAGAACAACGA
CGACCATCGTTCTGTGGATCTTCCTGCAGGGACCAGCGCAGGCGACATGAAACCAC
AACGCCAAAGACGTCTCTGCTGCATCTTTGCCATTCTTTGGTTCTGTTGTCTCGGTTA
ACAGTACAAATTGCAATGCACTGGCCGATTGAAAGAACTGCAATAAACGGAAAAA
AAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAG (SEQ ID NO:193)

Translation:
MQTAYWVMVMMVVVGFTVGGHVHQSHSPTSRSHGDDSIHDKTIHQHLFARLPLENND
DHRSVDLPAGTSAGDMKPQRQRRLCCIFAILWFCCLG (SEQ ID NO:194)

Toxin Sequence:
Leu-Cys-Cys-Ile-Phe-Ala-Ile-Leu-Xaa4-Phe-Cys-Cys-Leu-# (SEQ ID NO:195)

Name: S14.2
Species: striatus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTACAGCCCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGT
TTGGTGCCACACATCTTAACCCCACAGCATATCTTGCAAAGTCTGATTTCCCCTCTTC
GTTCTAACAACGGTCGTTCGAGTGGAGCACAAATATGCATCTGGAAGGTATGTCCA
CCATCCCCATGGAGACAACCACAAGAAATGATGAATGACATCAGACAACCGCCACA
ACTGTAGTACGACATCGTTGATACGACTTTAGCAAATATTTTAACATCACTGTGGTT
GTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTG
ATATCAGCTCTGCACTATGAAATAAAGCTGATGTGACAAACAAAAAAAAAAAAAAA
AAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:196)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPHILTPQHILQSLISPLRSNNGRSS
GAQICIWKVCPPSPWRQPQEMMNDIRQPPQL (SEQ ID NO:197)

Toxin Sequence:
Ser-Asn-Asn-Gly-Arg-Ser-Ser-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-Gln-Xaa3-Gln-Xaa1-Met-Met-Asn-Asp-Ile-Arg-Gln-Xaa3-Xaa3-Gln-Leu-^ (SEQ ID NO:198)

Name: Sx14.1
Species: striolatus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGACCCTCT
GTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGCCACGCATCTTAAC
CCCACAGCATACCTTGCGAAGTCCGACTTCCCTTCTTCGTTCTAACACCGGTGGTTC
GAGTGGAGCACAAATATGCATCTGGAAGGTATGTCCACCATCCCCATGGAGACGAT
CACAAGGAAAAAGATGAATGACGTCAGACAAGCGCCACAACTGTAGTACGACATC
GTTGATACGACTTCAGCAAGTATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTG
CTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCTGCCCTG
TGAAATAAAGCTGATG (SEQ ID NO:199)

Translation:
MQTAYWVMVMMMVWITDPLSEGGKLNDVIRGLVPRILTPQHTLRSPTSLLRSNTGGSS
GAQICIWKVCPPSPWRRSQGKR (SEQ ID NO:200)

Toxin Sequence:
Ser-Asn-Thr-Gly-Gly-Ser-Ser-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-Arg-Ser-Gln-# (SEQ ID NO:201)

Name: Sx14.2
Species: striolatus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGTTTGGTGCCACACATCTTAAC
CCCACAGCATATCTTGCAAAGTCTGATTTCCCCTCTTCGTTCTAACAACGGTCGTTC
GAGTGGAGCACAAATATGCATCTGGAAGGTATGTCCACCATCCCCATGGAGACGAT
CACAAGGAAAAAGATGAATGACGTCAGACAAGCGCCACAACTGTAGTACGACATC
GTTGATACGACTTCAGCAAGTATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTG
CTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTGATATCAGCTCTGCACTG
TGAAATAAAGCTGATG (SEQ ID NO:202)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPHILTPQHILQSLISPLRSNNGRSS
GAQICIWKVCPPSPWRRSQGKR (SEQ ID NO:203)

Toxin Sequence:
Ser-Asn-Asn-Gly-Arg-Ser-Ser-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-Arg-Ser-Gln-# (SEQ ID NO:204)

Name: Sx14.3
Species: striolatus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTAAAGACCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGG
TTTGGTGCCACACATCTTAACCCCACAGCATATCTTGCAAAGTCTGATTTCCCCTCTT
CGTTCTAACAACGGTCGTTCGAGTGGAGCACAAATATGCAACTGGAAGGTATGTCC
ACCATCCCCATGGAGACGACCACGAGGAAAATGATGAATGACATCAGACAACCGCC
ACAACTGTAGTACGACTTCGTTGATACGACTTTAGCAAATATTTTAACATCACTGTG
GTTGTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTA
CTGATATCAGCTCTGCACTATGAAATAAAGCTGATGTGACAAACAAAAAAAAAAAA
AAAAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:205)

Translation:
MQTAYWVMVMMMVWIKDPLSEGGKLNDVIRGLVPHILTPQHILQSLISPLRSNNGRSS
GAQICNWKVCPPSPWRRPRGK (SEQ ID NO:206)

Toxin Sequence:
Ser-Asn-Asn-Gly-Arg-Ser-Ser-Gly-Ala-Gln-Ile-Cys-Asn-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-Arg-Xaa3-Arg-# (SEQ ID NO:207)

Name: Sx14.4
Species: striolatus
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTACAGCCCCTCTGTCTGAAGGTGGTAAATTGAACGACGTAATTCGGGGT
TTGGTGCCACACATCTTAACCCCACAGCATATCTTGCAAAGTCTGATTTCCCCTCTTC
GTTCTAACAACGGTCGTTCGAGTGGAGCACAAATATGCATCTGGAAGGTATGTCCA
CCATCCCCATGGAGACAACCACAAGAAATGATGAATGACATCAGACAACCGCCACA
ACTGTAGTACGACATCGTTGATACGACTTTAGCAAATATTTTAACATCACTGTGGTT
GTGAAGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGTACTG
ATATCAGCTCTGCACTATGAAATAAAGCTGATGTGACAAACGAAAAAAAAAAAAAA
AAAAAAGTACTCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:208)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGLVPHILTPQHILQSLISPLRSNNGRSS
GAQICIWKVCPPSPWRQPQEMMNDIRQPPQL (SEQ ID NO:209)

Toxin Sequence:
Ser-Asn-Asn-Gly-Arg-Ser-Ser-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Val-Cys-Xaa3-Xaa3-Ser-Xaa3-Xaa4-Arg-Gln-Xaa3-Gln-Xaa1-Met-Met-Asn-Asp-Ile-Arg-Gln-Xaa3-Xaa3-Gln-Leu-^ (SEQ ID NO:210)

Name: Sl14.1
Species: sulcatus
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCTCTCTG
TCTGAAGGTGGTAAACCGAACGACGTCATTCGGGGTTTTGTGCCAGACGACTTAAC
CCCACAGCTTATCTTGCGAAGTCTGATTTCCCGTCGTCGTTCTGACAAGGATGTTGG
GAAGAGAATGGAATGTTACTGGAAGGCATGTAGACCCACGCTATCGAGACGACATG
ATCTTGGGTAAAAGATGAATGACGTCAGACAACAGCCACAACTATAGTATGACATC
GTTAATACGACTTCAGCAAATATTTTAACATCACTGTGGTTGTGAAGAAATCAGTTG

CTTTAAAAGATTGGATTTTTCCGTGTTTAAGAGTTGTACTGATATCAGCTCTGCCCTG
TGAAATAAAGCTGATG (SEQ ID NO:211)

Translation:
MQTAYWVMVMMMVWITASLSEGGKPNDVIRGFVPDDLTPQLILRSLISRRRSDKDVGK
RMECYWKACRPTLSRRHDLG (SEQ ID NO:212)

Toxin Sequence:
Arg-Ser-Asp-Lys-Asp-Val-Gly-Lys-Arg-Met-Xaa1-Cys-Xaa5-Xaa4-Lys-Ala-Cys-Arg-Xaa3-
Thr-Leu-Ser-Arg-Arg-His-Asp-Leu-# (SEQ ID NO:213)

Name: Tr14.1
Species: terebra
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGATAAATTGAACGACGTAATTCGGGGTTTGGTGCCAGATAACTTAG
CCCCACAGCTTGTTTTGCAAAGTCTGGATTCCCGTCGTCATCCTCACGGCATTCGTC
AGGATGGAGCCCAAATATGTATCTGGAAGATATGTCCACCATCCCCATGGAAACGA
CTTGGATCTTAAGAAAAGAAACAATTGACGTCAGACAACCGCCACAACTTGAGTAC
GACATCGTTAATACAACTTCAGCAAATATGAAATTTTCAGCATCACTGTGGTTGTGA
AGAAATCAGTTGCTTTAAAAGATTGGATTTGTCCTTGTTTAAGAGTTGTACTGATGT
CATCTCTGCACTGTGAAATAAAGCTGATGTGACAAACAAAAAAAAAAAAAAAAAA
GTACTCTGCGTTGTTACTCGAG (SEQ ID NO:214)

Translation:
MQTAYWVMVMMMVWITAPLSEGDKLNDVIRGLVPDNLAPQLVLQSLDSRRHPHGIRQ
DGAQICIWKICPPSPWKRLGS (SEQ ID NO:215)

Toxin Sequence:
His-Xaa3-His-Gly-Ile-Arg-Gln-Asp-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-
Ser-Xaa3-Xaa4-Lys-Arg-Leu-Gly-Ser-^ (SEQ ID NO:216)

Name: Tr14.2
Species: terebra
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGTGGATTACAGCCCCTCT
GTCTGAAGGTGATAAATTGAACGACGTAATTCGGGGTTTGGTGCCAGATAACTTAG
CCCCACAGCTTGTTTTGCATAGTCTGGATTCCCGTCGTCATCCTCACGGCATTCGTCA
GGATGGAGCCCAAATATGTATCTGGAAGATATGTCCACCATCCCCATGGAGACGAC
TTGGATCTTAAGAAAAGAAACAATTGACGTCAGACAACCGCCACATCTTGAGTACG
ACATCGTTAATACGACTTCAGCAAATATGAAATTTTCAGCATCACTGTGGTTGTGAA

GAAATCAGTTGCCTTAAAAGATTGGATTTGTCCTTGTTTAAGAGTTGTACTGATGTC
ATCTCTGCACTATGAAATAAAGCTGATGTGACAAACAAAAAAAAAAAAAAAAAAA
AGTACTCTGCGTTGTTACTCGAG (SEQ ID NO:217)

Translation:
MQTAYWVMVMMMVWITAPLSEGDKLNDVIRGLVPDNLAPQLVLHSLDSRRHPHGIRQ
DGAQICIWKICPPSPWRRLGS (SEQ ID NO:218)

Toxin Sequence:
His-Xaa3-His-Gly-Ile-Arg-Gln-Asp-Gly-Ala-Gln-Ile-Cys-Ile-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-
Ser-Xaa3-Xaa4-Arg-Arg-Leu-Gly-Ser-^ (SEQ ID NO:219)

Name: Vx14.1
Species: vexillum
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGATGGCCTACTGGGTGATGGTGATGATGATGG
TGTGGATTAAAGGCCCTGTGTCCGAAGGTGGTAAATTGAACGACGTAATTCGGGGT
TTGGTGCCAGACGACTTGACCCCAGTGTCTGCCTTGCATCATCCGGTTTCCCATCGT
CGGTCTCACAGCAGTAGTTTGTGGTGTGTATGTCCATTCAGGGTGTGTCCACCATGC
CATGGAAGATGACCTGGTCCCAAACCAACAAAATAACGTCAGACAACCGCCACAAC
TTTAGTACGACATCCCTTAATACGACTTCAGCAAGTATTTTAACATCACTATGGTGT
GATGAAATCAGTTGCTTTAAAAGATTGGATTTTTCCTTGTTTAAGAGTTGCACTGAT
AACAGCCCAGCAGTATGAAATAAAGTTGATGTGGCAAAAAAAAAAAAAAAAGTAC
TCTGCGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:220)

Translation:
MQMAYWVMVMMMVWIKGPVSEGGKLNDVIRGLVPDDLTPVSALHHPVSHRRSHSSS
LWCVCPFRVCPPCHGR (SEQ ID NO:221)

Toxin Sequence:
Ser-His-Ser-Ser-Ser-Leu-Xaa4-Cys-Val-Cys-Xaa3-Phe-Arg-Val-Cys-Xaa3-Xaa3-Cys-His-#
(SEQ ID NO:222)

Name: Vx14.2
Species: vexillum
Cloned: Yes

DNA Sequence:
GAATTCGCCCTTATGGATCCATGCAGACGGCCTACTGGGTGATGGTGATGATGATG
GTGTGGATTACAGCCCCTTTGTCTGAAGGTGGTAAACTGAACGATGTAATTCGGGGT
TTCGCGCTAGATGACTTAGCCCAAAGCCGTATTATGCAAAGTCTGGTTTTCAGTCAT
CAGCCTCTTCCAACGGCATCCATATGTATCTGGAAGATATGTCCACCAGACCCATGG
AGACGACATGATCTTCAGAAAAGTAACAAATGACGTCAGACAACCGCCACAACTTG

AATACAACATCATTAATACGACTTCAGCAAATATTTTAGCATCACTGTGATTGTTCG
GAAGTCAGTTGCTTTAAAAGATTGGATTTGTCCCTGTTGTATTGATGTCAACTCTGC
ACTATGAAATAAAGCTGATGTGACAAGCAAAAAAAAAAAAAAAAAAAAGTACTCTG
CGTTGTTACTCGAGCTTAAGGGCGAATTC (SEQ ID NO:223)

Translation:
MQTAYWVMVMMMVWITAPLSEGGKLNDVIRGFALDDLAQSRIMQSLVFSHQPLPTAS
ICIWKICPPDPWRRHDLQKSNK (SEQ ID NO:224)

Toxin Sequence:
Ile-Met-Gln-Ser-Leu-Val-Phe-Ser-His-Gln-Xaa3-Leu-Xaa3-Thr-Ala-Ser-Ile-Cys-Ile-Xaa4-Lys-Ile-Cys-Xaa3-Xaa3-Asp-Xaa3-Xaa4-Arg-Arg-His-Asp-Leu-Gln-Lys-Ser-Asn-Lys-^ (SEQ ID NO:225)

Name: Vx14.3
Species: vexillum
Cloned: Yes

DNA Sequence:
ATGCAGACGGCCTACTGGGTGATGGTGATGATGATGGTGGTGGGGTTCACCGTCGA
GAGTCACGTCCATCAGTCTCACAGTCCTACATCGCGCAGCCATGGTGATGACTCCAT
TCATGACAAGACGATTCATCAACATCTGTTTGCCCGTCTTCCTCTGGAGAACAACGA
CGACCATCGTTCTGTGGATCTTCCTGCAGGGACTAGCGCAGGCGACATGAAACCAC
AACGCCAGAAACGTTTCTGCTGCATCTTTGCCCCGATTCTTTTGTTCTGTTGTTTCGG
TTAACAGCACAAATTACACTGCACTGGCCGATTGAAAGAACTGCAATAAACGGTAA
AGCAAAAAAAAAAAAAAAAAAAAGTACTCTGCGTTGTTACTCGAG (SEQ ID NO:226)

Translation:
MQTAYWVMVMMMVVGFTVESHVHQSHSPTSRSHGDDSIHDKTIHQHLFARLPLENND
DHRSVDLPAGTSAGDMKPQRQKRFCCIFAPILLFCCFG (SEQ ID NO:227)

Toxin Sequence:
Phe-Cys-Cys-Ile-Phe-Ala-Xaa3-Ile-Leu-Leu-Phe-Cys-Cys-Phe-# (SEQ ID NO:228)

Xaa1 is Glu or γ-carboxy-Glu
Xaa2 is Gln or pyro-Glu
Xaa3 is Pro or hydroxy-Pro
Xaa4 is Trp, D-Trp or 6-bromo-[D or L] Trp
Xaa5 is Tyr, ^{125}I-Tyr, mono-iodo-Tyr, di-iodo-Tyr, O-sulpho-Tyr or O-phospho-Tyr
^ is free carboxyl or amidated C-terminus, preferably free carboxyl
# is free carboxyl or amidated C-terminus, preferably amidated
? is free carboxyl or amidated C-terminus

TABLE 2

Alignment of β-Superfamily Conotoxins (SEQ ID NO:)*

Type 2:			
T14.2	tulipa	----ZTDVLLEATLLTTPAPEQRLF**C**FWKS**C**WPRPYPWRRRDLN#	(229)
M14.1	magus	----ZTDVLLDATLLTTPAPEQRLF**C**FWKS**C**WPRPYPWRRRNLN#	(230)
G14.2	geographus	----ZTDVLLEATLLTTPAPEQRLF**C**FWKS**C**TWRPYPWRRRDLN#	(231)
T14.2	tulipa	-----------------------LF**C**FWKS**C**WPRPYPWRRRDLN#	(232)
M14.1	magus	-----------------------LF**C**FWKS**C**WPRPYPWRRRNLN#	(233)
G14.2	geographus	-----------------------LF**C**FWKS**C**TWRPYPWRRRDLN#	(234)
Type 3:			
Ge14.1	generalis	----------------SHSSSLW**C**V**C**PFRV**C**PP**C**H#	(235)
Vx14.1	vexillum	----------------SHSSSLW**C**V**C**PFRV**C**PP**C**H#	(236)
Type 4:			
Fd14.1	flavidus	---HDHGIRPKR----------VDI**C**NWRI**C**APNPLRRHDLKKGNN^	(237)
Em14.1	emaciatus	---HTHGIRPKG----------DGI**C**IWKV**C**PPDPWRRHRLKKRNN^	(238)
A14.1	aurisiacus	---HTHGIRPKG----------DGI**C**IWKV**C**PPDPWRRHHLKKRNN^	(239)
Tr14.1	terebra	---HPHGIRQDG----------AQI**C**IWKI**C**PPSPWKRLGS^	(240)
Tr14.2	terebra	---HPHGIRQDG----------AQI**C**IWKI**C**PPSPWRRLGS^	(241)
Ly14.2	litoglyphus	---HPHGIRQDG----------AQI**C**IWKI**C**PPSPWKRLGS^	(242)
Ly14.1	litoglyphus	---HPHGIRQDG----------AQI**C**IWKI**C**PPSPWRRLGS^	(243)

Type 5:		
Cn14.1	consors	---DRSDNGGSSG---------AQI**C**IWKV**C**PPSP^ (244)
Cn14.5	consors	---DRSDNGGSSG---------AQI**C**IWKV**C**PPSPWK^ (245)
Cn14.2	consors	---ARSDNGGSSG---------AQI**C**IWKV**C**PPSPWRRPQ# (246)
Sx14.1	striolatus	-----SNTGGSSG---------AQI**C**IWKV**C**PPSPWRRSQ# (247)
Sx14.3	striolatus	-----SNNGRSSG---------AQI**C**NWKV**C**PPSPWRRPR# (248)
Sx14.2	striolatus	-----SNNGRSSG---------AQI**C**IWKV**C**PPSPWRRSQ# (249)
Sx14.4	striolatus	-----SNNGRSSG---------AQI**C**IWKV**C**PPSPWRQPQEMMNDIRQPPQL^ (250)
S14.2	striatus	-----SNNGRSSG---------AQI**C**IWKV**C**PPSPWRQPQEMMNDIRQPPQL^ (251)
A14.3	aurisiacus	---LHSDSSDQKG---------AQI**C**IWKV**C**PPPPWR^ (252)
A14.2	aurisiacus	---LHSDSSDQKGGMNAWTGAGAQI**C**IWKV**C**PPPPWR^ (253)
A14.4	aurisiacus	---LRSDSSDQKGGMNASTGAGAQI**C**IWKV**C**PPSPWRRTQ# (254)
Cr14.1	circumcisus	---LRSDSSGQKG---------AQI**C**IWKV**C**PLSPWRRPQ# (255)
Cr14.2	circumcisus	---LRSDSSGQKG---------AQI**C**IWKV**C**PLSPWRRPQGKDE^ (256)
Ac14.1	achatinus	---LRSDNGGSSG---------AQI**C**IWKV**C**PPSPWRRPQ# (257)
Sm14.1	stercusmuscarum	---LGIGSSDQN----------AQI**C**IWKV**C**PPSP^ (258)
Cn14.3	consors	---NGSGSSNQKE---------AQL**C**IWKV**C**PPSPWR^ (259)
Cn14.4	consors	---NGSGSSNQKE---------AQL**C**IWKV**C**PPTPWR^ (260)
M14.2	magus	---NGSGSSNQKE---------AQL**C**IWKV**C**PPSPWR^ (261)
Nb14.2	nobilis	---NGSGSSNQKE---------AQL**C**IWKV**C**PPTPWR^ (262)
Type 6:		
Sl14.1	sulcatus	-------------RSDKDVGKRME-**C**YWKA**C**RPTLSRRHDL# (263)
Bk14.1	bocki	-------------RSDKDDPGGQE-**C**YWNV**C**APNQGDHMILRKKMNDDRQPPQL^ (264)
Bt14.1	betulinus	-------------RSDSDVREV-PV**C**SWKI**C**PP^ (265)
Ls14.1	loroisii	-------------RSDSDVREVYIL**C**IWKI**C**PPLP^ (266)

Type 7:		
Gd14.1	gladiator	--------------HPANVRQQGKICVWKVCPPWPVRSPGPQPKNK^ (267)
Gd14.2	gladiator	--------------HPANVRQQGKICVWKVCPPSPVRSPGPLPKNK^ (268)
Type 8:		
Ms14.2	musicus	GMGPGDLSLQKMFPSLALGPGGDVICRWKVCPPTPWKRLIK^ (269)
Ms14.3	musicus	GMVPGDLALQYLFPSLAFNP-PD-ICTWKVCPPPPWRRPKKITDVGQPPQL^ (270)
Ms14.1	musicus	GMVPGDLVLQYLFPSLAFSP-PD-ICTWKVCPPPPWRRPKKITDVRQPPQL^ (271)
Ms14.4	musicus	GMVPGDLVLQYLFPSLAFNP-PD-ICTWKVCPPPPWRRPKKITDVRQPPQL^ (272)
Type 9:		
Mi14.1	miles	ZQDQSPHHVCCAIGPVLPFCCVSWLHKLH^ (273)
Mi14.2	miles	--------LCCIFAPILWFCCH# (274)
Ra14.1	rattus	--------LCCIFA-ILWFCCL# (275)
Cp14.1	capitaneus	-------GFCCDFPPIFWFCCI# (276)
Mi14.4	miles	------ZGFCCVVIPILWFCCGGYRTNGTALAD^ (277)
Vx14.3	vexillum	--------FCCIFAPILLFCCF# (278)
Type 10:		
Sl14.2	sulcatus	--------------ZSGCRVPFELKCIWKFCTIYPSRPFASLEEKDECQTVTITVTWDF^ (279)
Ci14.1	cinereus	--------------SSGCSVSLGFKCFWKSCTVIPVRPFVSLEEENECQKVQISAVWGP^ (280)
Type 11:		
Pr14.1	parius	---------------------PPFSCSGLRGGCVLPPNLRPKFNKG# (281)
Pr14.2	parius	---------------------PPFSCAGLRGGCVLPPNLRPKFKE# (282)
Type 12:		
Wi14.1	wittigi	-------------SSDGSDPKAKKQCMWKRCIPDQSR---L-EEDE^ (283)
Ci14.4	cinereus	-------------SSDG---KAKKQCAWKTCVPTQWRRRDLKEKDE^ (284)
Ci14.3	cinereus	-------------SSDG---KAKRNCFWKACVPEQWRQRDPKEKDE^ (285)
Ci14.2	cinereus	-------------SSDG---KAKRNCFWKACVPEQWRQRDLKEKDE^ (286)

Type 13:		
Nb14.1	nobilis victor	-----------FRPAVKSRSRRAPP**C**VWKV**C**PAPPWLVTKRKQETSDY^ (287)
Nb14.3	nobilis skinneri	-----------FRPAVKSRSRRAPP**C**VWKV**C**PAPPWLVTKRKQETSDY^ (288)
Mi14.3	miles	-----------FRPAMQSRSGGMSL**C**LWKV**C**PAAPWLVAKRKQETSDY^ (289)
Miscellaneous:		
T14.1	tulipa	--------------HFNSVVPTVYI**C**MWKV**C**PPSP^ (290)
P14.2	purpurascens	------------------ZSEEEKI**C**LWKI**C**PPPPWRRS^ (291)
P14.1	purpurascens	------------------ESNGVEI**C**MWKV**C**PPSPWRRS^ (292)
Vx14.2	vexillum	--------IMQSLVFSHQPLPTASI**C**IWKI**C**PPDPWRRHDLQKSNK^ (293)
Mu14.1	muriculatus	--------IMQSLVFSHQPLPTASI**C**IWKI**C**PPDPWRRHDLQKSNK^ (294)
Pu14.1	pulicarius	------------------VRLRGQI**C**IWKV**C**PPLLQWIHPLVKR^ (295)
Pu14.2	pulicarius	------------------VRPRGQI**C**IWKV**C**PPLLQWIHPLVKR^ (296)
Pu14.3	pulicarius	-----------------PVRLRGQI**C**IWKV**C**PPLLQWIHPLVKR^ (297)
Mt14.2	mustelinus	-----------LVSHTSSKYPGVTF**C**PWKV**C**PPAPWRILGV^ (298)
Ba14.1	baileyi	---------------HSDSIILRGL**C**IWKV**C**EPPPQR^ (299)
Pl14.1	planorbis	--------------SSSNGLKRADL**C**IHKI**C**PPRYHQSQQ^ (300)
Lt14.2	litteratus	----------HRVFHLDNTYLKIPI**C**AWKV**C**PPTPWRRRDLKKRNK^ (301)
Lt14.1	litteratus	----SPVSTPYPEFHLDEPYLKIPV**C**IWKI**C**PPNLLRRRDLKKRNKVRQTTATT^ (302)
Ct14.1	coronatus	--------------LSDGRDWTGYI**C**IWKA**C**PRPPWIPPK# (303)
Cd14.2	chaldaeus	--------------LSEGRNSTVHI**C**MWKV**C**PPPPWRRPHGQR^ (304)
Cd14.1	chaldaeus	--------------LSEGRNSTVHI**C**TWKV**C**PPPPWRRPHGQR^ (305)
Eb14.1	ebraeus	--------------LSGGTYSRVDTCIWKVCPQSP^ (340)

* The W or F in the β-turn motif may be in the D or L configuration. Additionally, the K or F in the backbone may also be in the D or L configuration.

TABLE 3

Analogs and Truncations of β-Superfamily Conotoxins (SEQ ID NO:)

	Q663	ZCMWKRCIPDQSR^ (306)
	F531	VDICNWRICAPNPLR^ (307)
	βG-C1325	LCFX1KSCRPYPWR^ (308)
	βM1	LFCFX1WKSCWPRPYWR^ (309)
	βM2	LFCFX1KSCWPRPYPWR^ (310)
	βM3	LX2CFWKSCWPRPYWR^ (311)
	βM4	LX2CFX1KSCWPRPYWR^ (312)
	βM5	LX2CFWKSCWPR^ (313)
	βM6	LFCFX1KSCWPR^ (314)
	βM7	LX2CFX1KSCWPR^ (315)
	βM8	LX2CFWKSCW^ (316)
	βM9	LFCFX1KSCW^ (317)
	βM10	LX2CFX1KSCW^ (318)
	βM11	FCFX1KSCWPR^ (319)
	βM12	FCFWX3SCWPR^ (320)
	βM13	FCFX1FSCWPR^ (321)
	βM14	FCFWKSCWPR^ (322)
	βP2	ESNGVEICMX1KVCPPSPWRRS^ (323)
	βS1	MECYX1KACRPTLSR^ (324)
	βS12	FELKCIX1KFCTIYPSR^ (325)
	βS12b	FELKCIX1KFCTIYPSRPF^ (326)
	βT	TVYICMX1KVCPPSP^ (327)
	βA-CTL03	SDSSDQKAQICIX1KVCPPPPWR^ (328)
	βCn2	GAQICIX1KVCPPSPWR^ (329)
	βMs14.5	MFPSLALGPGGDVICRX1KVCPPTPWKRLIK^ (330)
	βFd-F531	VDICNX1RICAPNPLRRHDLKKGNN^ (331)
	βF531-dW	VDICNX1RICAPNPLR^ (332)
	βG14.1	RLFCFX1KSCTWRPYPWRRRDLN# (333)
	βD919 [1-4]	SLWCVCPFRVCPPCHGR^ (334)
	βD919 [2-4]	SLWCVCPFRVCPPCHGR^ (335)
	βGe [1-4]	SLWCVCPX2RVCPPCH# (336)
	βGe [2-4]	SLWCVCPX2RVCPPCH# (337)

X1 is D-Trp or L-Trp
X2 is D-Phe or L-Phe
X2 is D-Lys or L-Lys

EXAMPLE 2

Activity of Type 2 β-Superfamily Conopeptide on Tumor Cell Lines

[0108] Test Substance and Concentration: A β-M14.1 derivative, β-M14.1-D1 (LFCFXKSCWPRPYPWR (SEQ ID NO:309, where X is dW) was used for *in vitro* anti-tumor studies. The test compound was dissolved and diluted with sterile distilled water to obtain initial

working solutions of 10000, 1000, 100, 10, and 1 μM. In testing, 100-fold dilution was made in culture media to get final assay concentrations of 100, 10, 1, 0.1, and 0.01 μM.

[0109] Cell Culture Media: The culture medium used for the MCF-7 cell line was Minimum Essential Medium, 90%; Fetal Bovine Serum, 10%. The culture medium used for the MIA PaCa-2 cell line was Dulbecco's Modified Eagle's Medium, 90%; Fetal Bovine Serum, 10%. All media were supplemented with 1% Antibiotic-Antimycotic.

[0110] Cell Lines: The cell line MCF-7, which is a breast adenocarcinoma, pleural effusion, human, was obtained from the American Type Culture Collection (ATCC HTB-22). The cell line MIA PaCa-2, which is a pancreatic carcinoma, human, was obtained form the American Type culture Collection (ATCC CRL-1420). The tumor cells were incubated in an air atmosphere of 5% CO_2 at 3°C.

[0111] Chemicals: The sources of the chemicals were as follows: AlamarBlue (Biosource, USA), Antibiotic-Antimycotic (GIBCO BRL, USA), Dulbecco's Modified Eagle's Medium (GIBCO BRL, USA), Fetal Bovine Serum (HyClone, USA), Minimum Essential medium (GIBCO BRL, USA) and Mitomycin (Kyowa, Japan).

[0112] Equipment: Centrifuge 5810R (Eppendorf, Germany), CO_2 Incubator (Forma Scientific Inc., USA), Hemacytometer(Hausser Scientific Horsham, USA), Inverted Microscope CK-40 (Olympus, Japan), Spectrafluor Plus (Tecan, Austria), System Microscope E-400 (Nikon, Japan) and Vertical Laminar Flow (Tsao-Hsin, Taiwan).

[0113] Reference Methods: Ahmed et al. (1994), Boyd et al. (1989), Boyd et al. (1992).

[0114] Aliquots of 100 μl of cell suspension (about 2.5 x 10^3/well) were placed in 96-well microtiter plates in an air atmosphere of 5% CO_2 at 37°C. After 24 hours, 100 μl of growth medium and 2 μl of test solution, or mitomycin or vehicle (sterile distilled water), were added respectively per well in duplicate for an additional 72-hour incubation. The test compound, β-M14.1 derivative, was evaluated at concentrations of 100, 10, 1, 0.1 and 0.01 μM. At the end of incubation, the media in microplate were all removed, and then 200 μl of fresh media and 20 μl of 90% alamarBlue reagent were added to each well for another 6-hour incubation before detection of cell viability by fluorescent intensity. Fluorescent intensity was measured using a Spectraflour Plus plate reader with excitation at 530 nm and emission at 590 nm.

[0115] The measured results was calculated by the following formula:

$$PG\ (\%) = 100 \times (\text{Mean } F_{test} - \text{Mean } F_{time0})/(\text{Mean } F_{ctrl} - \text{Mean } F_{time0})$$

If (Mean F_{test} - Mean $F_{time}0$) < 0, then

$$PG\ (\%) = 100 \times (Mean\ F_{test} - Mean\ F_{time0})/(Mean\ F_{time0} - Mean\ F_{blank})$$

Where:

PG: percent growth

Mean F_{time0} = The average of 2 measured fluorescent intensities of reduced alamarBlue at the time just before exposure of cells to the test substance.

Mean F_{test} = The average of 2 measured fluorescent intensities of alamarBlue after 72-hour exposure of cells to the test substance.

Mean F_{ctrl} = The average of 2 measured fluorescent intensities of alamarBlue after 72-hour incubation without the test substance.

Mean F_{blank} = The average of 2 measured fluorescent intensities of alamarBlue in medium without cells after 72-hour incubation.

[0116] A decrease of 50% or more (≥50%) in fluorescent intensity relative to vehicle-treated control indicated significant growth inhibition, cytostatic or cytotoxic activity, and a semi-quantitative IC_{50}, TGI and LC_{50} were then determined by nonlinear regression using GraphPad Prism (GraphPad Software, USA).

[0117] The assays were used to detect changes in cell proliferation based on the ability of viable cells to cause alamarBlue to change from its oxidized (non-fluorescent, blue) to a reduced (fluorescent, red) form. With the results obtained from the alamarBlue reaction, cell proliferation can be quantified and metabolic activity of viable cells can be examined. The β-M14.1-D1 was tested for its effect upon the proliferation of 2 different human tumor cell lines, MCF-7 (breast) and MIA PaCa-2 (pancreas), at five final assay concentrations from 0.01 to 100 μM through serial l0-fold dilutions.

[0118] Based on the results obtained, the β-M14.1-D1 exhibited significant growth inhibition (≥ 50%) relative to the respective vehicle treated control group at concentrations between 10 μM to 100 μM in the 2 human tumor cells lines (Table 4). Significant activity was observed for the concurrently tested standard reference agent Mitomycin at < 10 μM (Table 1). Consequently, semi-quantitative determinations of estimated IC_{50} (50% inhibition concentration), TGI (total growth inhibition) and LC_{50} (50% lethal concentration) by nonlinear regression analysis were calculated (Table 5).

TABLE 4

Effect of Test Substance Tumor Cells

Treatment	Assay Name	Blank	Time$_0$	Percent Growth (Mean ± SEM, n=2) Vehicle	Concentration (μM) 100	10	1	0.1	0.01	0.001
PT# 1018911-ADD β-M14.1-D1	370000 Breast, MCF-7	-100	0	100	-43±11	102±14	87±9	88±12	100±8	[a]--
Mitomycin	370000 Breast, MCF-7	-100	0	100	--	-96±0	-38±16	5±12	88±8	95±7
PT# 1018911-ADD β-M14.1-D1	371700 Pancreas, MIA PaCa-2	-100	0	100	-14±9	109±2	100±4	102±6	102±3	--
Mitomycin	371700 Pancreas, MIA PaCa-2	-100	0	100	--	-93±2	-44±16	1±6	76±5	105±10

[a]--: Not tested

TABLE 5

Estimated IC_{50}, TGI and LC_{50} Values

Treatment	Prot. #	Assay Name	[a]IC_{50}	[b]TGI	[c]LC_{50}
PT# 1018911-ADD β-M14.1-D1	370000	Tumor, Breast, MCF-7	62 μM	81 μM	>100 μM
Mitomycin	370000	Tumor, Breast, MCF-7	0.035 μM	0.18 μM	0.93 μM
PT# 1018911-ADD β-M14.1-D1	371700	Tumor Pancreas, MIA PaCa-2	79 μM	95 μM	>100 μM
Mitomycin	371700	Tumor Pancreas, MIA PaCa-2	0.028 μM	0.15 μM	0.78 μM

[a] IC_{50} (50% Inhibition Concentration): Test compound concentration where the increase from time0 in the number or mass of treated cells was only 50% as much as the corresponding increase in the vehicle-control at the end of experiment.

[b] TGI (Total Growth Inhibition): Test compound concentration where the number or mass of treated cells at the end of experiment was equal to that at $time_0$.

[c] LC_{50} (50% Lethal Concentration): Test compound concentration where the number or mass of treated cells at the end of experiment was half that at $time_0$.

EXAMPLE 3

In Vitro Functional Activity of Type 2 β-Superfamily Conopeptide

[0119] The *in vitro* functional activity of β-M14.1-D1 with respect to somatostatin sst_2 and sst_5 was tested using the following assays.

Somatostatin sst_2 (Feniuk et al., 1993)

Tissue:	Duncan Hartley Guinea pig 325 ± 25 g
Vehicle:	0.1 mL Distilled Water
Incubation Time/Temp:	5 minutes @ 32 °C
Incubation Buffer:	Krebs, pH 7.4
Administration Volume:	10 µL
Bath Volume:	10 mL
Time of Assessment:	5 minutes
Quantitation Method:	Isometric (gram changes)
Significance Criteria -Ag:	≥50% Inhibition of contraction relative to somatostatin$_{28}$-responses
Significance Criteria -Ant:	≥50% Inhibition of somatostatin$_{28}$ relaxant response

Somatostatin sst_5 (Feniuk et al., 1993)

Tissue:	Duncan Hartley Guinea pig 325 ± 25 g
Vehicle:	0.1 mL Distilled Water
Incubation Time/Temp:	5 minutes @ 32 °C
Incubation Buffer:	Krebs, pH 7.4
Administration Volume:	10 µL
Bath Volume:	10 mL
Time of Assessment:	5 minutes
Quantitation Method:	Isometric (gram changes)
Significance Criteria -Ag:	≥50% Inhibition of contraction relative to somatostatin$_{28}$-responses
Significance Criteria -Ant:	≥50% Inhibition of somatostatin$_{28}$ relaxant response

[0120] Biochemical assay results are presented as the percent inhibition of specific binding or activity. All other results are expressed in terms of that assay's quantitation method. For primary assays, only the lowest concentration with a significant response judged by the assays' criteria, is shown. Primary screening in duplicate with quantitative data are shown where applicable for individual assays. Significant responses were noted in the primary assays shown in Table 6.

TABLE 6

Primary Tests[a]

Primary Tissue Assay	Tissue, gp	Conc.	Criteria	AG	ANT	EC_{50}/IC_{50}
Somatostatin sst_2	ileum	1 µM	≥50%	68%	ND	0.49 µM
Somatostatin sst_5	vas deferens	1 µM	≥50%	61%	ND	0.59 µM

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a A standard error of the mean is presented where results are based on multiple. independent determinations.
Gp = guinea pig; AG = Agonist; ANT = Antagonist; ND = Assay Test Not Done

EXAMPLE 4

Radioligand Binding Assay of Type 2 β-Superfamily Conopeptide

[0121] The radioligand binding activity of β-M14.1-D1 with respect to somatostatin sst_1, sst_2, sst_3 and sst_4 and sst_5 was tested using the following assays.

Somatostatin sst_1 (Liapakis et al., 1996; Patel and Srikant, 1994)

Source:	Human recombinant CHO-K1
Ligand:	0.1 nM ^{125}I Somatostatin-14
Vehicle:	0.4%DMSO
Incubation Time/Temp:	2 hours @ 25°C
Incubation Buffer:	25 mM Hepes, pH 7.4, 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.5% BSA
NonSpecific Ligand:	1 µM Somatostatin-14
K_d:	1.9 nM (historical value)
B_{max}:	0.5 pmol/mg Protein (historical value)
Specific Binding:	60% (historical value)
Quantitation Method:	Radioligand Binding
Significance Criteria:	≥50% of max stimulation or inhibition

Somatostatin sst_2 (Patel and Srikant, 1994)

Source:	Human recombinant CHO-K1
Ligand:	0.03 nM ^{125}I Somatostatin-14
Vehicle:	1% H_2O
Incubation Time/Temp:	4 hours @ 25°C
Incubation Buffer:	25 mM Hepes, pH 7.4, 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.5% BSA
NonSpecific Ligand:	1 µM Somatostatin-14
K_d:	0.034 nM (historical value)
B_{max}:	11 pmol/mg Protein (historical value)
Specific Binding:	90% (historical value)
Quantitation Method:	Radioligand Binding
Significance Criteria:	≥50% of max stimulation or inhibition

Somatostatin sst_3 (Liapakis et al., 1996; Patel and Srikant, 1994)

Source:	Human recombinant CHO-K1
Ligand:	0.1 nM ^{125}I Somatostatin-14
Vehicle:	0.4%DMSO
Incubation Time/Temp:	2 hours @ 25°C
Incubation Buffer:	25 mM Hepes, pH 7.4, 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.5% BSA
NonSpecific Ligand:	1 μM Somatostatin-14
K_d:	0.79 nM (historical value)
B_{max}:	1.1 pmol/mg Protein (historical value)
Specific Binding:	78% (historical value)
Quantitation Method:	Radioligand Binding
Significance Criteria:	≥50% of max stimulation or inhibition

Somatostatin sst_4 (Patel and Srikant, 1994)

Source:	Human recombinant CHO-K1
Ligand:	0.12 nM ^{125}I Somatostatin-14
Vehicle:	0.4%DMSO
Incubation Time/Temp:	2 hours @ 25°C
Incubation Buffer:	25 mM Hepes, pH 7.4, 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.5% BSA
NonSpecific Ligand:	1 μM Somatostatin-14
K_d:	0.87 nM (historical value)
B_{max}:	0.5 pmol/mg Protein (historical value)
Specific Binding:	60% (historical value)
Quantitation Method:	Radioligand Binding
Significance Criteria:	≥50% of max stimulation or inhibition

Somatostatin sst_5 (Greenwood et al., 1997; Patel and Srikant, 1994)

Source:	Human recombinant HEK-293 EBNA cells
Ligand:	0.1 nM ^{125}I Somatostatin-14
Vehicle:	1 % H_2O
Incubation Time/Temp:	60 minutes @ 37°C
Incubation Buffer:	50 mM Hepes, pH 7.4, 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.5% BSA
NonSpecific Ligand:	1 μM Somatostatin-14
K_d:	0.5 nM (historical value)
B_{max}:	1.2 pmol/mg Protein (historical value)
Specific Binding:	94% (historical value)
Quantitation Method:	Radioligand Binding
Significance Criteria:	≥50% of max stimulation or inhibition

[0122] Biochemical assay results are presented as the percent inhibition of specific binding or activity. All other results are expressed in terms of that assay's quantitation method. For primary assays, only the lowest concentration with a significant response judged by the assays' criteria, is shown. Primary screening in duplicate with quantitative data (e.g., IC_{50} ±

SEM, K_i ± SEM and nH) are shown where applicable for individual assays. In screening packages, primary screening in duplicate with semi-quantitative data (e.g., estimated IC_{50}, K_i and nH) are shown where applicable (concentration range of 4 log units). Significant responses were noted in the primary assays shown in Table 7.

TABLE 7

Primary Test

Primary Biochemical Assay	Species	Conc.	%Inh.	IC_{50}	K_i	n_h
Somatostatin sst_1	hum	0.1 μM	61	0.053 μM	0.05 μM	0.736
Somatostatin sst_2	hum	0.1μM	90	0.018 μM	9.35 nM	1.24
Somatostatin sst_3	hum	10 nM	61	6.14 nM	5.45 nM	0.714
Somatostatin sst_4	hum	10 μM	67	5.63 μM	4.95 μM	1.26
Somatostatin sst_5	hum	0.1 μM	61	0.082 μM	0.068 μM	0.961

hum = human

EXAMPLE 5

Radioligand Binding Assay of β-Superfamily Conopeptides

[0123] The radioligand binding activity of truncations of β-M14.1-D1 and other β-superfamily conopeptides with respect to somatostatin sst_1, sst_2, sst_3 and sst_4 and sst_5 was tested as described in Example 4. The peptides which were tested are set forth in Table 8. The significant responsers (≥50% inhibition or stimulation) are set forth in Table 9.

TABLE 8

Conopeptide	Type	Sequence (SEQ ID NO:)[a]
β-M14.1-6	2	LFCFX_1KSCWPR^ (314)
β-M14.1-9	2	LFCFX_1KSCW^ (317)
β-M14.1-10	2	LX_2CFX_1KSCW^ (318)
β-T14.1-D1	Misc	TVYICMX_1KVCPPSP^ (327)
β-Sl14.1-D1	6	MECYX_1KACRPTLSR^ (324)
β-Cn14.2-D1	5	GAQICIX_1KVCPPSPWR^ (329)

[a] X_1 is dW and X_2 is dF

TABLE 9

Primary Test

Primary Biochemical Assay	Species	Peptide	Conc.	%Inh.
Somatostatin sst_1	hum	β-Cn14.2-D1	10 μM	61
Somatostatin sst_3	hum	β-M14.1-6	0.1 μM	63
Somatostatin sst_3	hum	β-M14.1-9	0.1 μM	72
Somatostatin sst_3	hum	β-Sl14.1-D1	10 μM	82
Somatostatin sst_3	hum	β-Cn14.2-D1	10 μM	84
Somatostatin sst_4	hum	β-Cn14.2-D1	10 μM	60
Somatostatin sst_5	hum	β-M14.1-6	0.1 μM	57
Somatostatin sst_5	hum	β-M14.1-9	0.1 μM	55
Somatostatin sst_5	hum	β-M14.1-10	0.1 μM	65
Somatostatin sst_5	hum	β-T14.1-D1	10 μM	65
Somatostatin sst_5	hum	β-Sl14.1-D1	10 μM	86
Somatostatin sst_5	hum	β-Cn14.2-D1	10 μM	56

hum = human

EXAMPLE 6

Radioligand Binding Assay of Type 3 β-Superfamily Conopeptide

[0124] The radioligand binding activity of β-Ge14.1 D1 (SLWCVCPFRVCPPCH#; SEQ ID NO:335 with 1-3 fold), D919 (with 1-4 fold, SEQ ID NO:334) and D919 (with 2-4 fold, SEQ ID NO:335) with respect to melanocortin MC_3, MC_4, MC_5 and MCH (h) was tested using the following assays.

Melanocortin MC_3 (Schioth et al., 1995)

Source:	Human recombinant HEK-293 cells
Ligand:	0.035 nM ^{125}I NDP-αMSH
Vehicle:	0.4 % DMSO
Incubation Time/Temp:	60 min @ 37°C
Incubation Buffer:	25 mM HEPES-KOH, 0.2% BSA, pH 7.0,100 mM NaCl, 1 mM 1,10-phenanthroline, 1.5 mM CaCl2, 1 mM MgSO4, and one complete protease inhibitor tablet/100 ml
NonSpecific Ligand:	3 μM NDP-αMSH
K_d:	0.53 nM (historical value)
B_{max}:	6 pmol/mg Protein (historical value)
Specific Binding:	85% (historical value)
Quantitation Method:	Radioligand Binding
Significance Criteria:	≥50% of max stimulation or inhibition

Melanocortin MC_4 (Schioth et al., 1995)

Source:	Human recombinant HEK-293 cells
Ligand:	0.02 nM ^{125}I NDP-αMSH
Vehicle:	01 % H_20
Incubation Time/Temp:	2 hours @ 37°C
Incubation Buffer:	25 mM HEPES-KOH, 0.2% BSA, pH 7.0,100 mM NaCl, 1 mM 1,10-phenanthroline, 1.5 mM CaCl2, 1 mM MgSO4, and one complete protease inhibitor tablet/100 ml
NonSpecific Ligand:	3 μM NDP-αMSH
K_d:	0.5 nM (historical value)
B_{max}:	3.9 pmol/mg Protein (historical value)
Specific Binding:	90% (historical value)
Quantitation Method:	Radioligand Binding
Significance Criteria:	≥50% of max stimulation or inhibition

Melanocortin MC_5 (Schioth et al., 1995)

Source:	Human recombinant HEK-293 cells
Ligand:	0.035 nM ^{125}I NDP-αMSH
Vehicle:	1 % H_20
Incubation Time/Temp:	2 hours @ 37°C
Incubation Buffer:	25 mM HEPES-KOH, 0.2% BSA, pH 7.0,100 mM NaCl, 1 mM 1,10-phenanthroline, 1.5 mM CaCl2, 1 mM MgSO4, and one complete protease inhibitor tablet/100 ml
NonSpecific Ligand:	3 μM NDP-αMSH
K_d:	0.53 nM (historical value)
B_{max}:	6 pmol/mg Protein (historical value)
Specific Binding:	85% (historical value)
Quantitation Method:	Radioligand Binding
Significance Criteria:	≥50% of max stimulation or inhibition

MCH (h) (Chambers et al., 1999)

Source:	Human recombinant CHO cells
Ligand:	0.1 nM ^{125}I [Phe^{13}, Tyr^{19}]-MCH
Incubation Time/Temp:	60 min @ 22°C
NonSpecific Ligand:	1 μM NDP-αMSH
K_d:	0.05 nM (historical value)
Quantitation Method:	Radioligand Binding
Significance Criteria:	≥50% of max stimulation or inhibition

Melanocortin MC_1 (Siegrist et al., 1988)

Source:	Human recombinant CHO cells
Ligand:	0.05 nM ^{125}I NDP-αMSH
Incubation Time/Temp:	90 min @ 22°C
NonSpecific Ligand:	0.1 μM MCH
K_d:	0.62 nM (historical value)
Quantitation Method:	Radioligand Binding

Significance Criteria: ≥50% of max stimulation or inhibition

[0125] Biochemical assay results are presented as the percent inhibition of specific binding or activity. All other results are expressed in terms of that assay's quantitation method. For primary assays, only the lowest concentration with a significant response judged by the assays' criteria, is shown. Primary screening in duplicate with quantitative data (e.g., IC_{50} ± SEM, K_i ± SEM and nH) are shown where applicable for individual assays. In screening packages, primary screening in duplicate with semi-quantitative data (e.g., estimated IC_{50}, K_i and nH) are shown where applicable (concentration range of 4 log units). Significant responses were noted in the primary assays shown in Tables 10 and 11.

TABLE 10

Primary Test for β-Ge14.1-D1

Primary Biochemical Assay	Species	Conc.	%Inh.	IC_{50}	K_i	n_h
Melanocortin MC_5	hum	1 μM	71	0.294 μM	0.276 μM	0.762

hum = human

TABLE 11

Primary Test

Primary Biochemical Assay	Species	Peptide	Conc.	%Inh.
Melanocortin MC_3	hum	D919 [2,4]	10 μM	67
Melanocortin MC_4	hum	D919 [2,4]	10 μM	67
Melanocortin MC_4	hum	D919 [1,4]	10 μM	58
Melanocortin MC_5	hum	D919 [2,4]	10 μM	96
Melanocortin MC_5	hum	D919 [1,4]	10 μM	89
Melanocortin MC_1	hum	D919 [2,4]	10 μM	60
Melanocortin MC_1	hum	D919 [1,4]	10 μM	66
MCH (h)	hum	D919 [2,4]	10 μM	83
MCH (h)	hum	D919 [1,4]	10 μM	65

hum = human

[0126] It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed

herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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